CHEMICAL REVIEWS

Volume 95, Number 7 November 1995

Rationalizing the Regioselectivity in Polynitroarene Anionic σ-Adduct Formation. Relevance to Nucleophilic Aromatic Substitution

Erwin Buncel,*,[1a] Julian M. Dust,*,[1b] and François Terrier*,[1c]

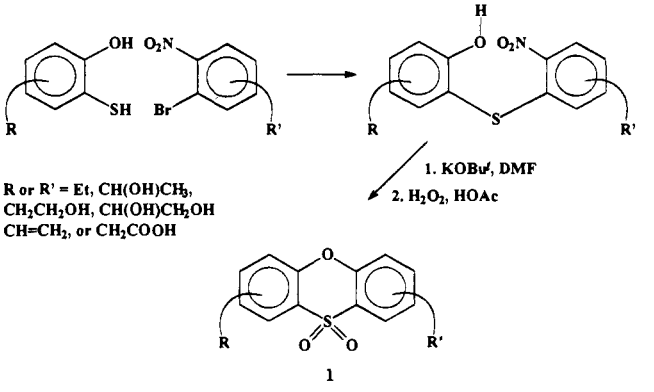
Department of Chemistry, Queen's University, Kingston, Ontario, Canada, K7L 3N6, Department of Chemistry, Sir Wilfred Grenfell College, Corner Brook, Newfoundland, Canada A2H 6P9, and Université de Versailles, SIRCOB Bâtiment Lavoisier, 45 Avenue des Etats-Unis, Versailles Cedex 78035 France

Received March 7, 1995 (Revised Manuscript Received July 20, 1995)

Contents

1. Mechanisms of Nucleophilic Aromatic Substitution: Synthetic Utility and Applications—Drug Research and Polymer and Environmental Chemistry

The synthetic chemistry of electron-deficient aromatics and heteroaromatics is circumscribed by the four major mechanisms of nucleophilic aromatic substitution: S_NAr,[2-4] $S_{RN}1$,[5,6] the Vicarious Nucleophilic Substitution (of hydrogen), VNS,[7,8] and substitution by Addition of Nucleophile with Ring Opening followed by Ring Closing or S_N(ANRORC).[9,10] The S_NAr displacement reaction forms the backbone of numerous important syntheses of pharmaceuticals and potential drugs as illustrated by the preparation of a series of possible hypotensive drugs, the 3-(X-amino)-1,2,4-benzothiadiazine 1-oxides,[11] a series of antidepressant monoamino oxidase (MAO) inhibitors (**1**, sequence 1), the phenoxathiin 10,10-dioxides,[12] and preparation of the dibenzo[1,4]dioxincarboximides, which are prospective antitumor agents.[13] Many of



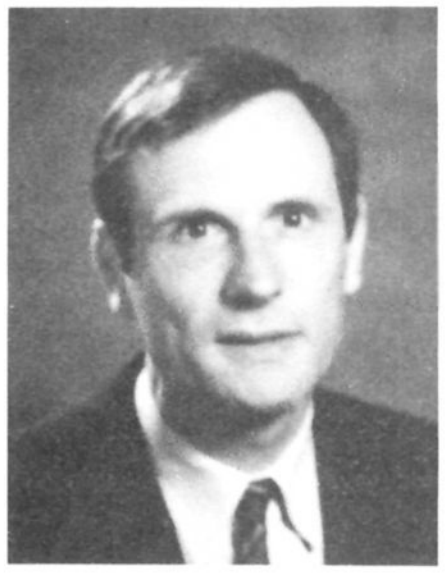
Sequence 1

these syntheses (sequence 2) rely upon the presence of a nitro group in the aromatic moiety that can be displaced[4,14] with concomitant cyclization.[15] In an interesting recent example,[15c,d] it was shown that 2-nitro-6-X-toluenes react with tetrabutylammonium fluoride to give the nitroanions, which do not dimerize as expected,[16] but undergo intermolecular Michael addition to the α,β-unsaturated ester (sequence 3). In the case of 2-nitro-6-(trifluoromethyl)toluene this is followed by an intramolecular fluoride ion-catalyzed cyclodenitration to give the substituted indan.[15d] Further, several classes of bioactive agents, including examples of herbicides, fungicides, and pesticides, as well as drugs, require the presence of a nitro function on an aromatic or heteroaromatic ring,[17] whether to enhance acidity or increase susceptibility to attack by (cellular) thiol[18] or amino groups.[19,20]

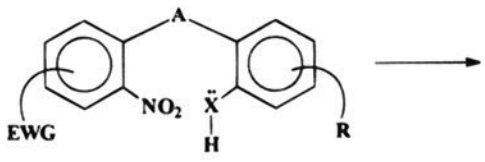
0009-2665/95/0795-2261$15.50/0

Erwin Buncel was born in Czechoslovakia, but educated in England. He received the B.Sc. and Ph.D. degrees from the University of London, the latter under the supervision of Professor Alwyn Davies in the School of Sir Christopher Ingold. He then crossed the ocean for a postdoctoral year at the University of North Carolina with Joe Bunnett, where he was introduced to the fascinating world of aromatic azo ether hydrolysis. Going up North as a National Research Council of Canada postdoctoral fellow to work with Arthur Bourns at McMaster University, enlightened him to the clues that isotopic substitution held in reaction mechanisms. Buncel then returned to the United States for a brief period as a research chemist at American Cyanamid Central Research Labs in Stamford, CT, where he learned much from the insight of Edwin Ullman. In 1962, opportunity arose to accept a faculty position at Queen's University, with promotions to Associate (1966) and Full Professor (1970). At Queen's, Buncel developed various career-long avenues of investigation in physical organic, bioorganic, and bioinorganic chemistry, with the devotion of 50 graduate students and numerous postdoctoral fellows, who made possible the publication of about 250 research papers, as well as a number of book chapters, review articles, and two books. Collaborations with colleagues in different countries have been especially rewarding. Buncel was the recipient of the Syntex Award of the Canadian Society for Chemistry in 1985. Of great challenge have been his editorial activities, for the Canadian Journal of Chemistry (1981–1993) and currently for the Journal of Labelled Compounds and Radiopharmaceuticals. Buncel looks to continuing challenges that the world of chemistry holds.

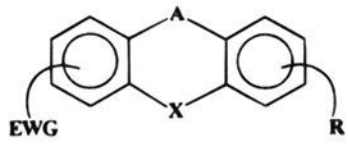
Julian Dust completed his B.Sc.(Hons) in 1978 at the University of Waterloo, in southwestern Ontario, but then traveled east to Mt. Allison University, where he studied free radical chemistry of sterically-hindered aromatics with Professor Ross Barclay. In 1982 he traveled farther east to Dalhousie University where, under the guidance of Professor Don Arnold, he received a M.Sc. for a thesis that defined the $\sigma^{\bullet}_{\alpha}$ substituent scale for benzylic radicals. Changing direction, Dust moved west to Queen's University, and as a student of Professor Erwin Buncel, commenced a study of Meisenheimer complexes, including those formed by novel ambident polynitroheteroaromatics (i.e. super-electrophiles). This research led to a Ph.D. in 1987 and it continues to be a focus of his effort. His postdoctoral work at University of Alabama in Huntsville with Professor Milton Harris sparked another continuing interest: preparation, application, and mechanistic investigation of poly(ethylene glycol) derivatives. In 1989 he settled in Corner Brook, the western-most city in the eastern-most province in Canada, Newfoundland. There he accepted an Assistant Professorship at Sir Wilfred Grenfell College (Memorial University); he was granted tenure in 1994 and was promoted to the rank of Associate Professor in 1995.



François Terrier was born in Gisors, France, in 1940. He obtained his Ph.D. in 1968 from the University of Paris. After postdoctoral research with Prof. Claude F. Bernasconi at the University of California, Santa Cruz, he was appointed Professor at the University of Rouen, while assuming the direction of a research group at the Ecole Nationale Supérieure de Chimie de Paris. In 1991, he moved to the new University of Versailles, where he holds a Professorship of Organic Chemistry and is Head of the Department of Chemistry. Beyond the fields described in this paper, Terrier's current research interests include the synthesis and reactivity of neutral super-electrophilic heteroaromatics, mechanistic studies of nucleophilic displacements by α-effect nucleophiles, and proton-transfer processes at carbon. In addition to about 150 research papers, as well as a number of chapters in books and review articles, Terrier is the author of a recent book covering all aspects of Nitroactivated Nucleophilic Aromatic Displacements (VCH Publishers, New York, 1991).



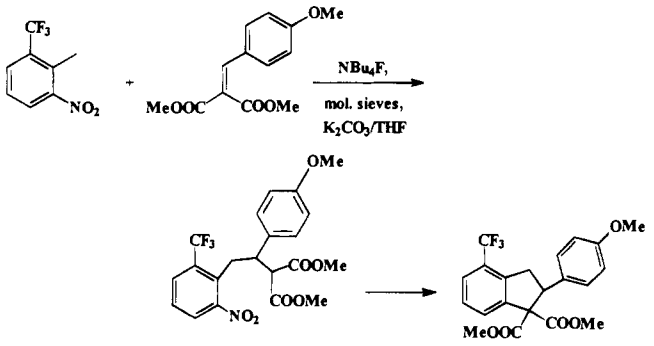
EWG = electron withdrawing group
R = NO_2, CN, COOR, COOH



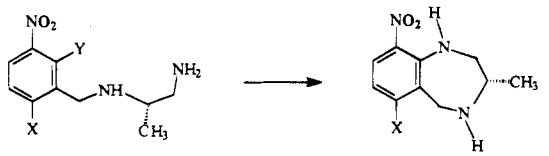
A = S, X = O	phenoxanthiins (*cf.* 1)
A = NR', X = S	phenothiazines
A = X = O	dibenzodioxins
A = X = S	thianthrene
A = X = NR'	dihydrophenazines

Sequence 2

Nitro substitution of an aromatic moiety clearly activates the ring to nucleophilic attack and displacement. Parker and Coburn made use of this feature in their preparation of two nitrobenzodiazepines (sequence 4) that are useful intermediates in the preparation of HIV-I inhibitors.[21] In this synthesis the initial diamine derivatives undergo *regioselective* intramolecular nucleophilic substitution in which a halogen, activated by the *ortho* nitro group, is displaced concurrent with cyclization. Most recently, Beugelmans prepared a series of vancomycin models by means of an S_NAr *macrocyclization* reaction.[22] Here a nitro group has served to activate the ring to fluoride displacement.



Sequence 3



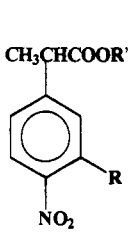
X = Y = Cl
or
X = Y = F

Sequence 4

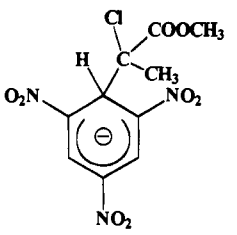
In fact in biochemistry generally, proteins are labeled and protein residues characterized by reaction with Sanger's reagent (1-fluoro-2,4-dinitrobenzene)[23,24] or with 4-chloro- or 4-fluoro-7-nitrobenzofurazan (NBD chloride or NBD fluoride, respectively);[25] these reactions are known to follow the S_NAr mechanism. Recently, there has been increased interest in the labeling of bioactive agents with radioactive ^{18}F for mechanistic studies, as well as diagnostic tests;[26,27] the S_NAr route provides access to these aromatic compounds via reaction with $^{18}F^-$. This current interest[28,29] is further illustrated by a recent review that concerns the use of fluoride as a nucleophile in the S_NAr reaction.[30] On the other hand, the VNS pathway can offer alternative routes to biologically significant fluoroarenes. For example, a preparation of fluorinated benzoic acids, which may be intermediates in the synthesis of antibacterial quinolines, has been patented; it involves treatment of a variety of 1-chloro-3-nitrobenzenes with carbanions that contain leaving groups, presumably followed by oxidation of the resultant toluenes.[31]

The VNS reaction has also proved valuable in the synthesis of pharmaceuticals[32] and natural products.[33] Interestingly, while Stahly and co-workers[34] obtained good yields of the expected 2-(4-nitroaryl)-propanoate esters (**2**) from the VNS reaction of a series of 2-substituted 1-nitrobenzenes with the carbanion generated from some 2-chloropropanoate esters they failed to effect the necessary elimination step (*cf.* Scheme 1) in the same reaction with 1,3,5-trinitrobenzene (TNB) as substrate; instead a carbon-centered Meisenheimer adduct (**3**)[35,36] was isolated.[37]

With the carbanion of chloromethyl phenyl sulfone, TNB reacts to yield a trisubstituted VNS product,[38a] but only monoaddition occurs when the trifluoromethyl carbanion is used and no elimination occurs.[39] Clearly, the products arising from the interaction of suitably substituted carbanions with nitroarenes depend not only upon competition between the VNS and S_NAr mechanisms; the outcome of the VNS



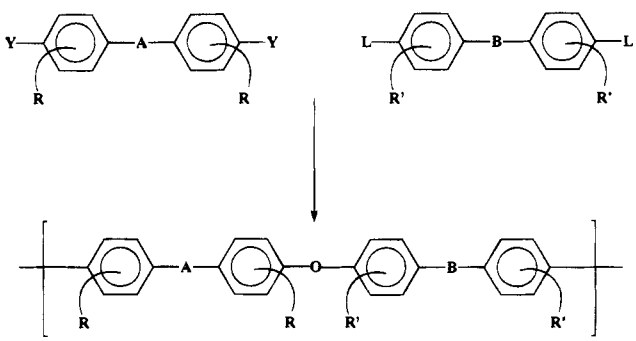
2



3

reaction is also sensitive to the nature of both electrophile and attacking carbanion, as well as choice of conditions.[38]

Electrophilic polymer derivatives, including picryl cellulose,[40] and the picryl[41] and dinitrophenyl ethers[42] of poly(ethylene glycol) (PEG) have been prepared through exploitation of the S_NAr reaction. Displacement of a nitro group has also been used to graft "living" PEG to nitro-substituted polystyrene in the preparation of graft copolymers.[43] Not only is S_NAr displacement of a variety of groups (Cl, F, NO_2, etc.) the standard procedure for the syntheses of aromatic polyether sulfones, polyether ketones, and polyetherimides,[44] as well as polyalkyl aryl ethers,[45] but has also been used to end-cap polyether ketones with arylethynyl termini, suitable for later cross-linking of the polymer.[46] Although the mechanism of these



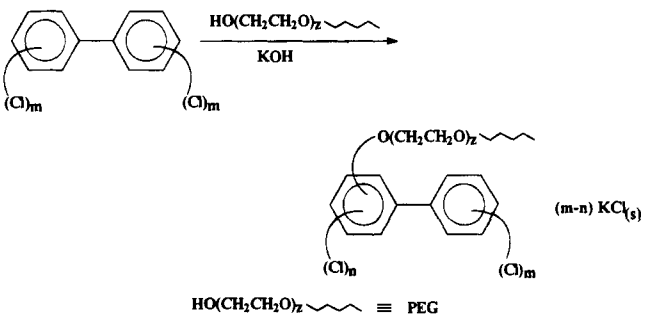
$Y = O^{\ominus}M^{\oplus}$
A *or* B = O, S, SO_2, CO, CH_2, $C(CH_3)_2$, N=N, $\overset{O}{\nwarrow}$N=N
R *or* R' = CH_3, CH_2CH_3, Ph, NO_2

Sequence 5

polymerizations and derivatizations has been taken to be S_NAr[43-46] there is recent evidence that the $S_{RN}1$ mechanism may compete when less activated substrates are used in the polymerization. Thus, in the polymerization of 1,3-bis(4-fluorobenzoyl)benzene or its chloro counterpart with the dianion of 1,4-hydroquinone the first substrate yielded high molecular weight polyaryl ether ketone, whereas the latter gave only oligomeric material.[47] Addition of a radical scavenger to the 1,3-bis(4-chlorobenzoyl)benzene/1,4-hydroquinone dianion reaction system to suppress the competing $S_{RN}1$ pathway then led to formation of high molecular weight polymer, presumably by the S_NAr route.[47,48]

In environmental chemistry, nucleophilic aromatic substitution also plays a significant role. Thus, although the toxic polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs) arise via several routes from industrial sources,[49] analytical standards have been prepared by the S_NAr cyclization route from polychlorinated phenoxyphenols[50] or by

the reaction of chlorocatechols with polychloronitrobenzenes[51,52] (*cf.* sequence 2). Moreover, S_NAr displacement has been used to remediate the environment, as in the detoxification of waste oil at a former wood treatment plant[53a] by reaction of the pentachlorophenol- and PCDD-containing fluid with PEG and KOH.[53] A similar approach was used by Brunelle and Singleton to dechlorinate polychlorinated biphenyls (PCBs); in this situation the S_NAr product PEG ethers were isolated.[54]



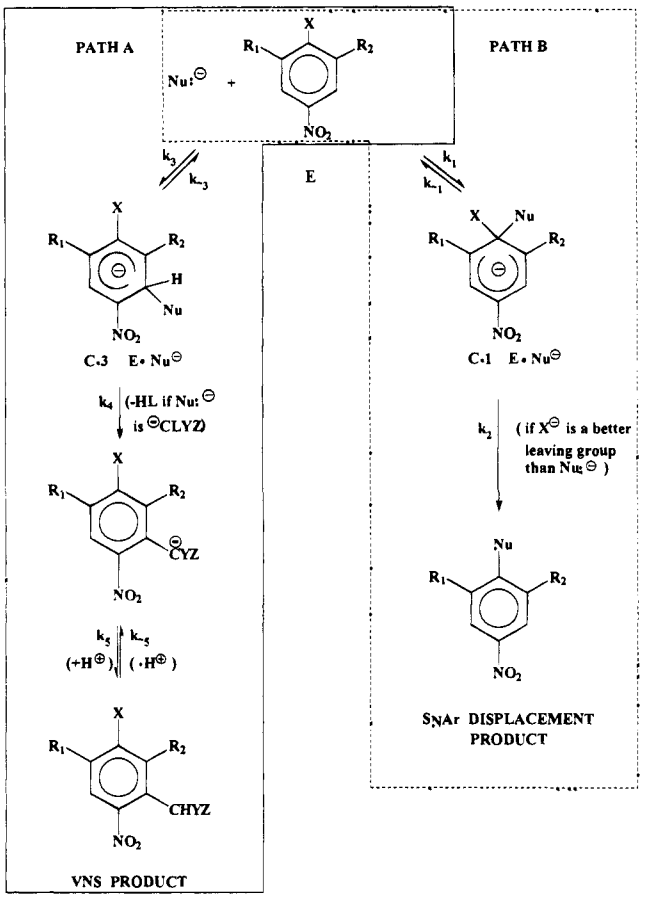
Sequence 6

In summary, the study of the mechanisms of aromatic substitution of electron-deficient aromatics and heteroaromatics, including those factors that effect choice of mechanistic path and the regioselectivity within a given mechanism, can have a major impact in such important areas as drug synthesis, polymer research, and environmental chemistry. It is our contention that a thorough understanding of the underlying mechanisms (and attendant regioselectivity associated with a given mechanism) will be of value in the practical choice of conditions, solvents, and even nucleophiles, used in the preparation of new drugs and polymers, in the preparation of analytical standards for environmental investigations, and in the choice of procedures used in environmental amelioration.

2. The Dichotomy between S_NAr and VNS Reactions: The Importance of the Regioisomeric Meisenheimer Adducts

The key intermediate in both the S_NAr and VNS mechanisms is the negatively-charged σ-bonded adduct, commonly termed a Meisenheimer complex,[2,35,36] (*cf.* Scheme 1), and for this reason the two pathways may compete in appropriate systems.[7a] As a result of the formidable electron-withdrawing power of the nitro function, nitro substitution also favors formation of donor–acceptor complexes,[55] aryl carbanions,[56] and radical anions.[57] In a controversial proposal[58,59] Bunton and co-workers have advanced a unified mechanism of nucleophilic aromatic displacement in which even highly activated nitroaromatics, such as picryl chloride, would react via a pathway involving donor–acceptor complexes, radical anion–radical pairs, aryl carbanions, as well as regioisomeric Meisenheimer adducts.[60] Note, nonetheless, that even in this unified approach the C-1 Meisenheimer adduct is the preeminent intermediate that leads directly to substitution product. All other species are formed either prior to or in competition with Meisenheimer adduct formation.[60]

Scheme 1



Scheme 1 illustrates both the VNS (path A, left-hand branch, solid-boxed portion) and S_NAr (path B, right-hand branch, dashed-line boxed portion) reaction pathways according to the traditional formalism of two-electron (spin-paired) nucleophilic attack. In principle, then, a nucleophile ($Nu:^-$) could react at either the C-1 (*ipso*) position or at the C-3 unsubstituted position of a typical 1-X-2,4,6-trinitrobenzene electrophile (E; $R_1 = R_2 = NO_2$, Scheme 1). Attack at C-1 of such a substrate that bears a good leaving group, X, leads to formation of a metastable C-1 Meisenheimer adduct (C-1 E·Nu^-) that decomposes by expulsion of X^- to yield a 1-Nu-2,4,6-trinitrobenzene (Nu–E′) in an overall S_NAr displacement (path B, eq 1):

$$E + Nu:^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{C-1 E·Nu:}^- \xrightarrow[-X^-]{k_2} Nu\text{–E}' \quad (1)$$

Conversely, if the nucleophile is a carbanion that itself contains a good leaving group (L) at the carbanion center (i.e. in Scheme 1, $Nu:^- = {}^-CLYZ$, where Y and/or Z are electron withdrawing) attack at C-3, formation of the C-3 Meisenheimer adduct (C-3 E·Nu^-), followed by β-elimination of HL gives rise to an α-substituted 3-X-2,4,6-trinitrotoluene derivative (Nu′–E), after protonation of the initial benzylic carbanion (^-Nu–E) during workup. This overall process, as elucidated by Makosza and coworkers,[7] is the VNS reaction (path A). Thus:

$$E + Nu:^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \text{C-3 E·Nu}^- \xrightarrow{k_4} {}^-Nu\text{–E} \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} Nu'\text{–E} \quad (2)$$

The dichotomy is made apparent if one considers partitioning of attack of a suitable carbanion (e.g.

$^-$CLYZ) between C-1 and C-3. Attack at C-1 could lead to rapid ejection of X^- from the C-1 adduct. Attack at C-3 could lead to equally rapid elimination of HL from the C-3 adduct. It should be noted that in partitioning between VNS and S_NAr products of 1-fluoro-4-nitrobenzene, yield of VNS products increased with increasing amount of added nonnucleophilic base,[38b] pointing out the importance of the elimination step in the mechanism. Other conditions including choice of nucleophile and substrate can also influence the ratio of VNS and S_NAr products formed in competing systems.[7,38] Notwithstanding the role of the relative kinetics of the two rearomatization steps, the choice of reaction pathway (S_NAr vs VNS) would be largely dictated by the regioselectivity of adduct formation: C-1 vs C-3 (eq 3).

$$\text{C-3 E·Nu}^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \text{E} + \text{Nu:}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{C-1 E·Nu}^- \quad (3)$$

In this review we shall consider the regioselectivity of adduct formation for polynitroarenes in detail.

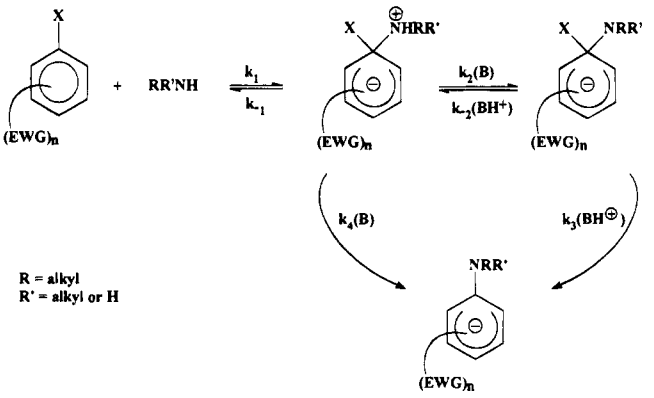
3. Regioselectivity in Meisenheimer Adduct Formation

3.1. Scope of Behavior

If X in Scheme 1 is a relatively poor nucleofuge, such as methoxyl, both the C-1 and C-3 regioisomeric Meisenheimer adducts, arising from C-1 and C-3 attack of a wide variety of nucleophiles, may be observable depending upon solvent and temperature.[61,62] Thus, as a prototypical electron-deficient aromatic, 1-methoxy-2,4,6-trinitrobenzene (2,4,6-trinitroanisole, TNA) has been shown to form a C-3 Meisenheimer adduct (C-3 TNA·OMe^-) as the kinetically preferred adduct with methoxide ion. This adduct gives way with time to the thermodynamically more stable C-1 adduct (C-1 TNA·OMe^-).[62] However, TNA reacts with cyanide ion in the exact inverse way: the C-1 TNA·CN^- adduct is now the product of kinetic control, while the 1,3 TNA·CN^- adduct is thermodynamically favored.[63] Azide ion attacks only at C-1 to yield the C-1 TNA·N_3^- adduct,[64] in apparent agreement with the behavior of other simple nitrogen nucleophiles; in the reaction of *n*-butylamine with TNA the C-1 adduct was the only Meisenheimer complex definitively identified in the low-temperature (−40 °C) flow NMR spectrum even though the initial spectrum was recorded relatively rapidly (0.44 s).[65]

Generalizations concerning the regioselectivity of Meisenheimer complexation with amines may be premature. In this regard, Crampton and co-workers have recently explored the reactions of simple amines, such as *n*-butylamine, piperidine, and pyrrolidine in dimethyl sulfoxide (DMSO) solvent, with ethyl picryl sulfide,[66] phenyl 2,4-dinitronaphthyl sulfide, phenyl 2,6-dinitro-4-(trifluoromethyl)phenyl sulfide,[67] and most recently, with the ethyl and *iso*propyl picryl ethers that are directly analogous to TNA.[68] In all cases, except the amine−phenyl 2,4-dinitronaphthyl sulfide and amine−phenyl 2,6-dinitro-4-(trifluoromethyl)phenyl sulfide reaction systems, the C-3 adducts could be detected by stopped-flow spectrophotometry; kinetic results suggest that attack at C-3 is faster than C-1 attack, but displacement occurs via the thermodynamically more stable C-1 adduct. However, the situation is complicated by possible changes in rate-determining step, notably whether proton transfer from the initially formed C-1 zwitterionic adduct is wholly or partly rate limiting. Thus, in the reaction of ethyl picryl sulfide with *n*-butylamine[66] a first-order dependence of rate on amine concentration was noted and formation of the C-1 zwitterionic Meisenheimer adduct (*cf.* Scheme 2) constitutes the slow step in the overall displacement. With the same substrate a correlation of rate with the square of pyrrolidine concentration indicated that base catalysis operated and that proton transfer from the zwitterionic adduct was involved in the rate-determining decomposition of the intermediate.

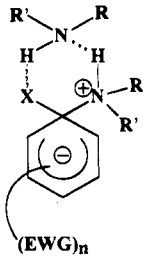
Scheme 2



The general features of the mechanism for S_NAr displacement by amines in DMSO are widely accepted[36b,66-69] and are outlined in Scheme 2 (excluding C-3 attack). Attack of the amine on C-1 of the electron-deficient aromatic leads to formation of a zwitterionic intermediate (k_1, Scheme 2). At this stage, either (1) the zwitterionic adduct and the "N-neutral" C-1 amine adduct equilibrate ($K_2 = k_2/k_{-2}$), followed by rate-determining general acid-catalyzed loss of the leaving group (k_3), or (2) rate-limiting proton transfer from the zwitterionic Meisenheimer adduct to base (k_4) accompanies rapid ejection of the leaving group, X. The former pathway is the specific base−general acid (SB−GA) mechanism advanced by Bunnett and co-workers[2,70] supported by a classic study of Bunnett and Orvik[71] and found in a number of systems.[72-74] Attack of the amine at C-1 (k_1) may itself be rate determining under the condition that the rate constant for decomposition of the zwitterionic adduct back to amine and electron-deficient substrate (k_{-1}) be much less than the rate constants (k_2 or k_4, Scheme 2) for decomposition of the zwitterionic adduct either to the N-neutral amine adduct or to displacement product. Here base catalysis would not be expected.

The situation is even more complex in low polarity aprotic solvents such as benzene,[75] ethyl acetate, and tetrahydrofuran,[76] where deprotonation of the zwitterionic intermediate may involve an amine dimer in competition with free amine[75b] or two molecules of free amine acting in concert.[77] In some cases the kinetics have also been shown to be consistent with an amine dimer acting as nucleophile in the initial

step of the mechanism.[78] This final proposal would lead naturally to the formation of a zwitterionic intermediate in which a further molecule of amine is complexed to both the attached ammonium center and to the leaving group, a structure (**4**) reminiscent of that advanced by Capon and Rees[79] for amine-catalyzed decomposition of the "standard" zwitterionic intermediate (Scheme 2) in low polarity aprotic solvents such as benzene and cyclohexane. Clearly,



4

since the nature of the mechanism and the identity of the rate-determining step are sensitive to the steric and electronic nature of the amine involved[36b,69b] as well as the structure of the electron-deficient substrate and the properties of the solvent, a definitive statement concerning regioselectivity of amines in Meisenheimer complex formation must await the systematic compilation of rate constants for initial attack on the substrates (at C-1 and C-3).

Consideration of Meisenheimer complexation with other electrophiles that are structurally related to TNA does not immediately clarify the situation, but does reinforce the view that a wide range of regioselectivity applies to these reactions. Thus, Crampton and co-workers have provided kinetic evidence for formation of a C-1 methoxide adduct of 2,4,6-trinitrobenzyl chloride; they did not detect any C-3 to C-1 isomerization,[80] rather proton abstraction from the benzylic position competes with nucleophilic attack at the C-1 ring site. Nonetheless, the same group has reported reaction of other alkoxides at C-3 of 2,4,6-trinitrobenzyl chloride with either subsequent rearrangement to the more stable C-1 adducts or proton abstraction again from the benzylic position;[81] the preference for C-3 attack is in accord with the behavior of sulfite ion with the same substrate.[82] Cyanide ion forms a C-1 adduct with 2,4,6-trinitrobenzaldehyde as the product of both kinetic and thermodynamic control.[83] However, with a wide range of nitroarenes Makosza and co-workers have found that carbanions, suitably substituted with leaving groups, give rise preferentially to products formed from attack at unsubstituted ring position via adducts analogous to the C-3 adducts cited above.[7] In this regard, Crampton et al. have recently quantified the kinetic preference of cyano and nitro carbanions for C-3 with a variety of 1-X-2,4,6-trinitrobenzenes.[84] Evidently, a modest change in either nucleophile or electron-deficient aromatic can fundamentally alter the pattern of regioselectivity found in Meisenheimer complexation.

3.2. Regioselectivity of Ambident Phenoxide Ion with TNA

With such a diversity of regioselectivities, what behavior would one expect to find in the reaction of the ambident (C- and O-) nucleophile, phenoxide ion, with TNA? In monitoring the TNA–PhO^- reaction system by 400 MHz ^1H NMR spectroscopy we have found that as an O-nucleophile phenoxide reacts with TNA to yield only the 1,1-TNA·OPh^- adduct.[85] The C-1 Meisenheimer O-adduct is the first complex formed regardless of whether the system is observed at ambient temperature in DMSO, a solvent generally recognized to enhance Meisenheimer complex formation,[2,35,36,86] or at low temperature (−40 °C) in acetonitrile/glyme (1:1 v/v), a novel medium whose utility we have demonstrated in a number of low-temperature NMR studies.[85,87,88] The conclusion, that the C-1 TNA·OPh^- O-adduct is favored by both kinetics and thermodynamics over its C-3 counterpart, is supported by the stopped flow UV–vis kinetic study of this reaction detailed by Bernasconi and Muller,[89] who also observed the C-1 adduct as the first species formed in solution, but did not detect the C-3 analog. In the 50–90% DMSO/H_2O (v/v) media examined, the reaction proceeded to give the C-3 TNA·OH^- adduct and eventually yielded picrate anion. Further, although not detected or not thoroughly characterized spectroscopically, the TNB·OPh^- adduct,[90b,c,91,92] which is a model for any putative C-3 TNA·OPh^- adduct, has recently been unambiguously assigned under the low-temperature acetonitrile/glyme reaction conditions.[90a] Because the TNB·OPh^- adduct may be observed at −40 °C in MeCN/glyme (1:1), it is reasonable to think that the C-3 TNA·OPh^- adduct would have been observed *if it had formed.* On these grounds, the C-1 TNA·OPh^- adduct is the product of both kinetic and thermodynamic control within the manifold of O-centered Meisenheimer complexes that phenoxide hypothetically could form.

The result in the TNA–PhO^- system is all the more striking because in DMSO at room temperature the "standard" formation of the C-3 TNA·OMe^- adduct as a kinetic product, followed by isomerization to the more stable C-1 TNA·OMe^- adduct, occurs concurrent with the formation (and later decomposition) of the C-1 TNA·OPh^- adduct. These methoxide adducts arise from solvolytic reactions in which adventitious water is implicated (eqs 4–6);[85,90a] reaction of TNA with water, via either an S_N2-type displacement or an S_NAr process or both, gives rise to methanol and picrate anion ($PicO^-$, eq 4):

$$\mathrm{TNA} + \mathrm{H_2O} \rightarrow \mathrm{PicO^-} + \mathrm{MeOH} + \mathrm{H^+} \qquad (4)$$

The MeOH so generated, in the presence of excess phenoxide ion (PhO^-), provides an equilibrium concentration of methoxide ion (MeO^-) from which the C-1 and C-3 TNA·OMe^- adducts are

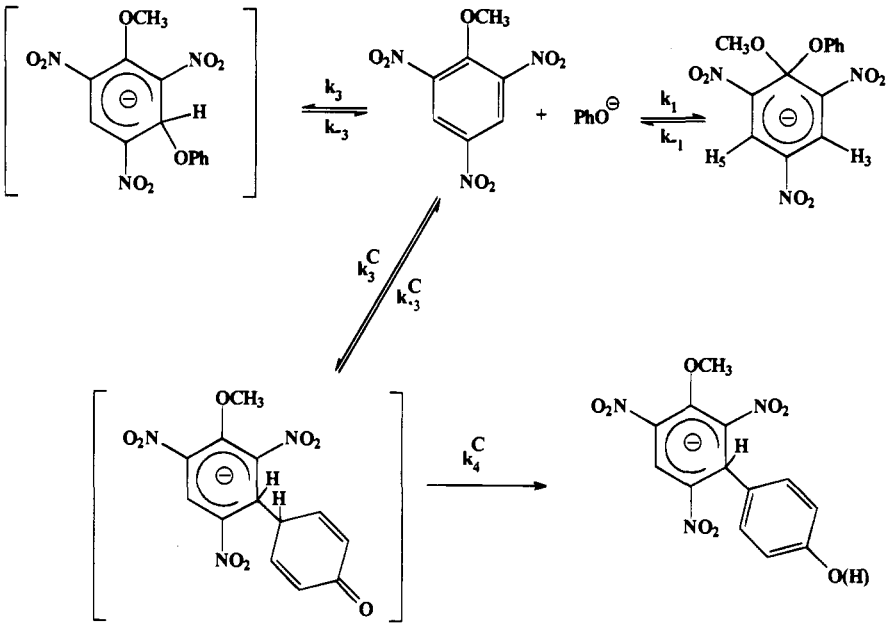
$$\mathrm{PhO^-} + \mathrm{MeOH} \rightleftarrows \mathrm{PhOH} + \mathrm{MeO^-} \qquad (5)$$

derived (eqs 4–6).

$$\mathrm{TNA} + \mathrm{MeO^-} \rightleftarrows (\text{C-3} + \text{C-1})\ \mathrm{TNA{\cdot}OMe^-} \qquad (6)$$

Similarly, equilibration between phenoxide and water present in the solvent could also give rise to the TNA adducts derived from hydroxide attack. Regardless, the salient point is that *the reaction of TNA with PhO^-, acting as an O-nucleophile, does not*

Scheme 3

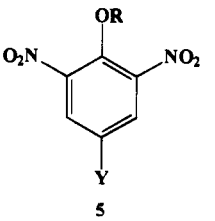


conform to the C-3 to C-1 isomerization pathway typically found for alkoxides.

With time the C-1 TNA·OPh$^-$ adduct gave way to the C-3 carbon-centered Meisenheimer adduct, C-3 TNA·PhO(H)$^-$, in which the phenoxy moiety is bonded through the *para* carbon position and the state of ionization of the phenoxyl OH is uncertain. This adduct is formed plausibly by a two-step process (Scheme 3) in which initial attack gives rise to a metastable quinoidal adduct, which is not observed, followed by a rearomatization step (k_4^C) that yields the C-3 phenoxide C-adduct, which is observed. This rearomatization step confers effective irreversibility on the process of C-3 TNA·PhO(H)$^-$ carbon-adduct formation. Because C-3 attack of PhO$^-$, as a C-nucleophile, is irreversible, then, it has been unclear as to whether formation of the C-3 C-adduct is favored thermodynamically over formation of the hypothetical C-1 C-adduct in this system. A similar difficulty arises in assessing the thermodynamics of Meisenheimer adduct formation between acetonate anion and 1-phenoxy-, 1-ethoxy-, or 1-chloro-2,4,6-trinitrobenzene (picryl chloride)[61g] under basic conditions. In these cases where the media are alkaline, C-3 adducts are formed irreversibly and, in some cases, react further to give *meta*-bridged adducts.[61j] The relative stability of the C-3 and C-1 carbon adducts, therefore, has been uncertain in these systems, although it is well known that enolate C-adducts of TNB do revert to starting electrophile and enolate (or enol) in neutral (or acidic) solution.[61k]

4. Classification of Patterns of Regioselectivity

In view of the wide range of behavior encountered in the reaction of nucleophiles with electron-deficient aromatics it has become clear that the various patterns of regioselectivity should be classified. We have proposed a general classification tied to qualitative free energy profiles.[85,87,90a,93] Thus, the regioselectivity exhibited by methoxide with TNA involves the following kinetic relationships between the forward and reverse rate constants for attack at C-3 (i.e. k_3 and k_{-3}, respectively) and the forward and reverse rate constants for attack at C-1 (k_1 and k_{-1}; Scheme 1): $k_3 > k_1$ and $k_{-3} > k_{-1}$. The latter kinetic inequality follows from the observed thermodynamic preference, i.e. K_1, the equilibrium constant for formation of the C-1 adduct, is greater than K_3, the equilibrium constant for formation of the C-3 adduct. The qualitative free energy profile for the sequence found in the TNA–MeO$^-$ system[62,85] is given in Figure 1 as K3T1 (*kinetic* preference for attack at *C-3* combined with *thermodynamic* preference for formation of the *C-1* adduct). For clarity, energy differences in K3T1 and the other profiles are exaggerated. A quantitative profile has been determined for the TNA–MeO$^-$ system by Bernasconi[61f] in methanol solvent and by Terrier[36d] in DMSO/MeOH. Although K3T1 applies explicitly to the TNA–MeO$^-$ system, it should be viewed as a generalized profile that accounts for the regioselectivity found in a range of electron-deficient aromatic–nucleophile systems, including the reactions of alkoxides with picryl ethers.[61,62] In this regard, Table 1 illustrates the different classes of regioselectivity displayed by selected triactivated ethers, including TNA (*cf.* structure **5**), in reaction with a range of nucleophiles.



5

K1T1 describes the case where formation of the C-1 adduct is favored by both kinetics and thermodynamics. The TNA–PhO$^-$ system, where phenoxide ion acts as an O-nucleophile, fits this case,[85] as do a number of related systems (Table 1). Here, $k_1 > k_3$ and $K_1 > K_3$ and, likely, $k_{-3} > k_{-1}$. By similar logic, K3T3 applies to the inverse situation, where the C-3

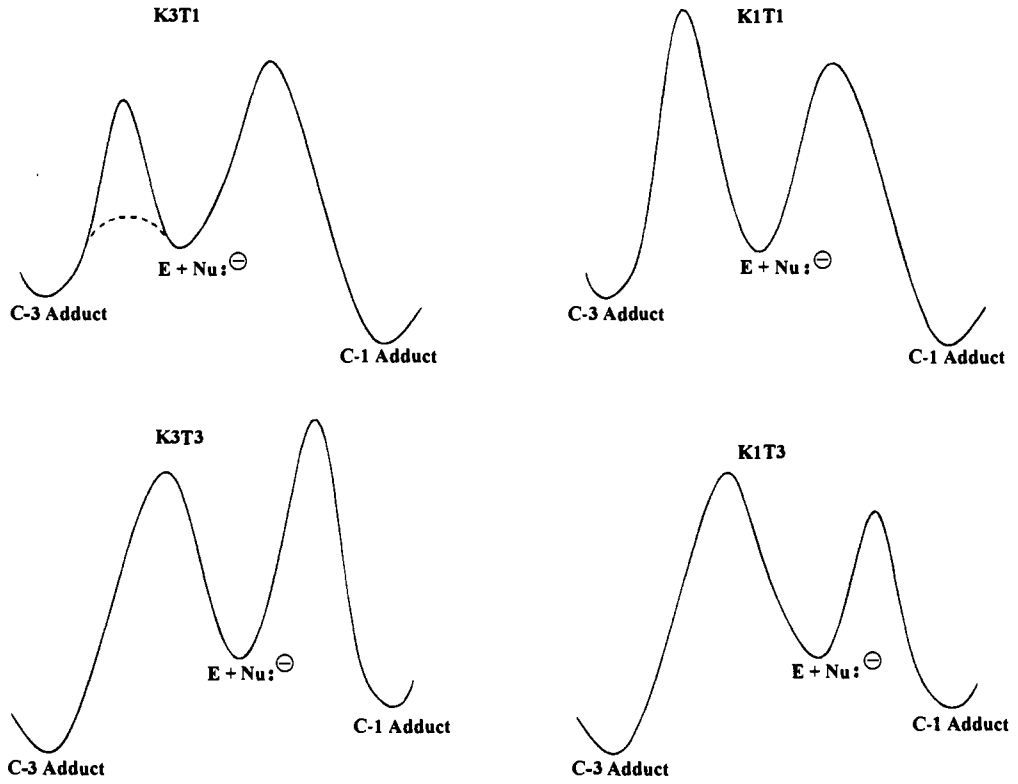


Figure 1. Qualitative comparative energy–reaction coordinate profiles for the four general patterns of regioselectivity. Barrier heights and relative stabilities are exaggerated for clarity. K3T1 describes those systems in which formation of the *C-3* adduct is the product of *kinetic* control, but the *C-1* adduct is the *thermodynamic* product. In the K1T1 profile the C-1 adduct is favored by both kinetics and thermodynamics. Conversely, K3T3 represents the situation where the C-3 adduct is doubly preferred: by kinetics and by thermodynamics. K1T3 profile describes the inverse behavior from that indicated by K3T1; now, the C-1 adduct is favored kinetically, but the C-3 adduct is the most stable product. The profiles are described in further detail in the text.

Table 1. Kinetic and Thermodynamic Control in Meisenheimer Adduct Formation with Selected Triactivated Aryl Ethers

nitroarene Y[a]	R	nucleophile	regioselectivity	ref(s)
NO_2	CH_3 (TNA)	$^-OCH_3$	K3T1	61e–g,62,85
(TNA)		$^-OC_2H_5$	K3T1	96
(TNA)		$^-$OPh (as O-nucleophile)	K1T1	85,89
(TNA)		$^-N_3$	K1T1	64
(TNA)		n-$BuNH_2$[b,c]	K1T1	65
(TNA)		CN^-	K1T3	63
(TNA)		$^-$OMes[d]	K1T3	87
NO_2	C_2H_5	$^-OC_2H_5$	K3T1	97
NO_2	$CH_3/C_2H_5/CH(CH_3)_2$	$^-OC_2H_5$	K3T1	98
NO_2	$CH(CH_3)_2$	$^-OCH(CH_3)_2$	K3T1	99
NO_2	PEG[e]	n-$PrNH_2$[c,f]	K1T1	41
NO_2	Ph	$^-$OPh (as O-nucleophile)	K1T1	100
NO_2	Mes[d]	t-$BuNH_2$[c,g]	K1T1	101
NO_2	Mes[d]	$^-$OMes[d]	K1T3	100
NO_2	SC_2H_5	$^-SC_2H_5$	K1T3[h]	94
SO_2CF_3	CH_3	$^-OCH_3$	K3T1	102
SO_2CF_3	CH_3	$^-OCH_3$	K3T1	103
CN	CH_3	$^-OCH_3$	K3T1	103
CF_3	CH_3	$^-OCH_3$	K3T1	103

[a] See structure 5. [b] 1-Butylamine. [c] See also ref 68. [d] Mes = 2,4,6-trimethylphenyl. [e] PEG = poly(ethylene glycol). [f] 1-Propylamine. [g] *tert*-Butylamine. [h] See also ref 95.

adduct is doubly favored: $k_3 > k_1$, $K_3 > K_1$ and, as shown in Figure 1, $k_{-1} > k_{-3}$. The relative activation barriers and stabilities of the regioisomeric adducts for these cases are shown in Figure 1.

Arguably the most interesting pattern of regioselectivity is that represented by the K1T3 profile. This energy diagram (Figure 1) shows the opposite regioselectivity to that of K3T1. Now C-1 attack is kinetically favored, while the C-3 adduct is the product of thermodynamic control: $k_1 > k_3$, $K_3 > K_1$, and $k_{-1} > k_{-3}$. This regioselectivity has previously been found for CN^- reacting with TNA[63] and for ethanethiolate reacting with the structural analog, picryl ethyl sulfide.[94] Work by Crampton and Stevens[95] confirms the observed preference for C-1 attack for ethanethiolate and thioglycolate anions on picryl ethyl ether on the basis of NMR measurements. However, they determined a fine balance

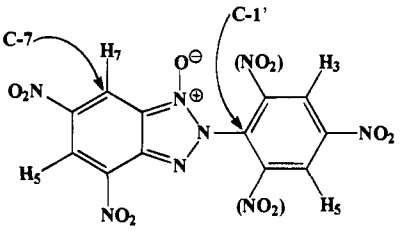
between attack at the two sites based on assumptions applied to their kinetic results in aqueous DMSO. More recently we have extended the number of examples of K3T1 behavior by observing it in the reaction of sterically hindered 2,4,6-trimethylphenoxide (mesitoxide, $MesO^-$) with TNA,[87] as monitored by 400 MHz ^1H and ^{13}C NMR (−40 °C, MeCN/glyme 1:1).

Although Table 1 clearly delineates the various types of possible regioselectivity, a cautionary note should be sounded. A significant factor that could limit confidence in the results in some systems arises from the ambiguity imposed by the possibility of having rate constants of widely different magnitudes. If we consider the K3T1 profile, for example, and if for a given system the kinetic conditions $k_3 > k_1$ but also $k_{-3} \gg k_{-1}$ both hold, as shown by the dotted lines in Figure 1 (K3T1 profile), it may not be possible to observe the C-3 adduct owing to the time scale of the experiment employed. The regioselectivity, then, would appear to fit the K1T1 profile. This ambiguity, which also applies to the other qualitative profiles, would justify the reexamination of several systems with "state of the science" techniques. In the TNA−PhO^- system, however, both fast stopped-flow kinetics[89] and low-temperature NMR studies[85] concur with an assignment of K1T1 to the regioselectivity shown by phenoxide as an O-centered nucleophile with TNA.

A comment should also be made concerning the apparent lack of K3T3 behavior compiled in Table 1. As pointed out above, in many systems carbon adducts are formed irreversibly and so any inherent thermodynamic preference for C-1 or C-3 of TNA, for example, has been obscured, even though the kinetic preference for C-3 attack (or attack at an unsubstituted position in other less activated electrophiles) by carbanions is well documented.[7,38] Recent AM1 calculations[93] of the thermodynamic stability of adducts (based on the enthalpy change for formation of the adducts) formed by hydroxide and methide ions, as archetypal O- and C-nucleophiles respectively, with a range of nitroarenes, support the view that carbon nucleophiles form C-3 adducts of TNA (and the corresponding adducts with other nitroarenes) as the products of thermodynamic control. Therefore, where kinetic preference for attack of a C-nucleophile at an unsubstituted position has been demonstrated, as in the reaction of TNA with acetonate anion[61g] and with PhO^-, as a C-nucleophile,[85] the regioselectivity is likely to be of the K3T3 type.

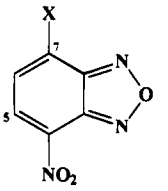
Except where paucity of data precludes it, this classification can be extended to a variety of related systems, most obviously the 2,4,6-trinitrobiphenyl−MeO^- system which shows K3T1 regioselectivity,[104] the TNT−CN^- system for which there is evidence of K3T3 behavior,[83] as well as the TNT−alkoxide systems studied by a number of groups[81,105−108] which either fit the K3T3 description or show K3T1 behavior. In some of the TNT systems benzylic carbanion formation competes with alkoxide attack at C-1, so that the relative thermodynamic stability (C-1 vs C-3) of the alkoxide adducts is uncertain. Regardless of the difficulties inherent in assessing the regioselectivity in amine systems, the methyl 4-methoxy-3,5-dinitrobenzoate−piperidine and −pyrrolidine systems,[109] follow the K1T1 profile and, less ambiguously, so does the picryl fluoride−F^- system.[110]

Note, also, that comparative energy profiles similar to those given in Figure 1 have been used to describe the regioselectivity found in the 2-(nitroaryl)-4,6-dinitrobenzotriazole 1-oxide series (**6**) where nucleophilic attack may partition between the C-7 superelectrophilic site, leading to a relatively persistent C-7 Meisenheimer adduct, or to C-1′ which yields only a transient (unobserved) C-1′ adduct that decomposes in an overall S_NAr displacement.[111]

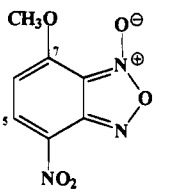


6

It is also possible to consider the reactions of the 7-halo-4-nitrobenzofurazans (**7**)[112] and 7-methoxy-4-nitrobenzofuroxan(**8**)[113] with methoxide ion. In both



7

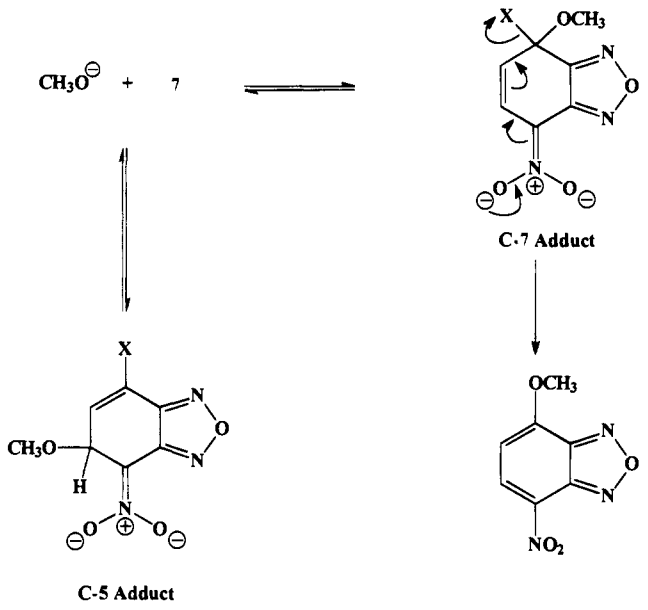


8

systems, formation of C-5 MeO^- adducts preceded formation of the thermodynamically more stable C-7 adducts (or the products arising immediately from their decomposition). This behavior (C-5 → C-7 isomerization) is analogous to that found in the TNA−MeO^- system (C-3 → C-1 isomerization) and labeled K3T1. Thus, for the 7-X-4-nitrobenzofurazan and 7-methoxy-4-nitrobenzofuroxan systems the regioselectivity may be described as K5T7, numbering the sites of attack as usual (Scheme 4), although the K3T1 qualitative profile (Figure 1) remains an apt illustration of the reaction energetics. Interestingly, in the 7-methoxy-4-nitrobenzofuroxan−MeO^- reaction system, only the C-7 adduct could be observed by room temperature NMR spectroscopy; it was necessary to cool the system to −15 °C prior to start of the reaction in order to detect and characterize the C-5 adduct as the product of kinetic control.[113] The same K5T7 regioselectivity applies to 4-nitrobenzofuroxan reacting with MeO^- [114]even though here the C-7 position is also unsubstituted. Subsequent rearrangement, via a formal internal redox, of the C-7 adduct leads to formation of 7-methoxy-4-nitrobenzofurazan as the final product.[113] Clearly, parallels may be drawn between the regioselectivity found in the triactivated benzene and the heteroaromatic systems, but it would be premature to force the analogy further, at present.

Such classification may more properly be applied to ambident electrophilic systems such as the 2,2′,4,4′,6,6′-hexanitrostilbene−RO^- and 2,2′,4,4′,6,6′-hexanitrobibenzyl−RO^- systems studied by Cramp-

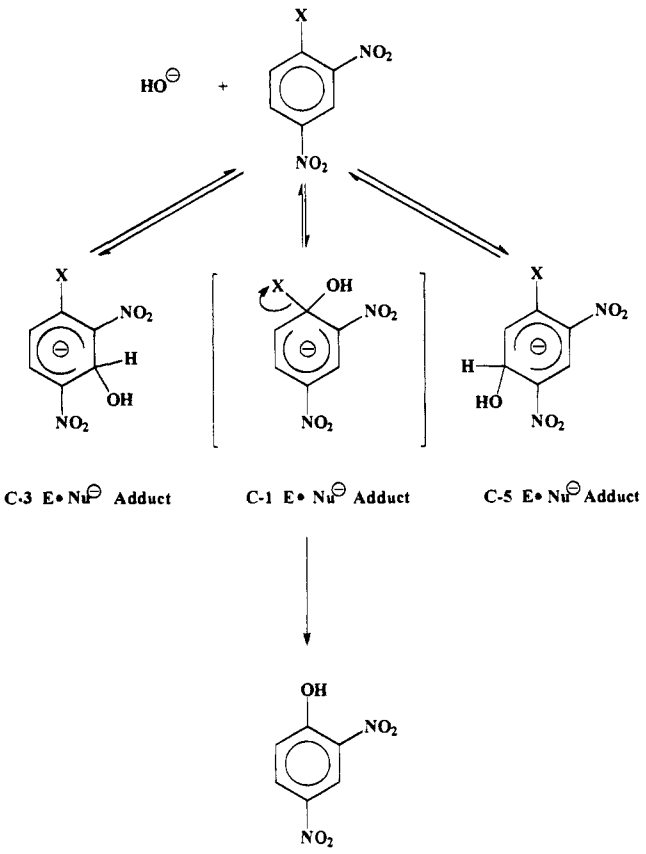
Scheme 4



ton and co-workers.[116,117] In the case of the former reaction system, alkoxides show kinetic preference for attack at a C-3 site and thermodynamic preference for C-1 attack, in accord with the K3T1 profile, even though the ultimate product of reaction of alkoxides with the hexanitrostilbene may result from nucleophilic attack on the linking double bond of the stilbene.[116] On the other hand, the 2,2′,4,4′,6′,6′-hexanitrobibenzyl–alkoxide systems show almost the full range of possible behavior. ^{1}H NMR studies with MeO^- show that C-3 monoadduct formation is kinetically preferred, but is followed by C-1,1′ diadduct formation; a transient C-1,3′ diadduct was also postulated on the basis of the NMR evidence. However, in methanol solvent stopped-flow kinetic studies were consistent with formation of the C-1 monoadduct alone; there was no evidence for diadduct formation or for formation of a benzylic anion (or dianion).[117] Full analysis of the regioselectivity found in ambident systems will likely require both direct spectroscopic observation and kinetic studies.

Extension of the classification scheme to diactivated electrophiles, such as the 1-X-2,4-dinitrobenzenes, would require the addition of at least one other axis to the relevant energy profiles for the different possible reaction pathways, i.e. for attack at C-1, C-3, *and* C-5. In this regard, the reaction 1-halo-2,4-dinitrobenzenes with OH^- in aqueous DMSO involves formation of both C-5 and C-3 adducts, but the final 2,4-dinitrophenoxide product presumably arises from the thermodynamically preferred, albeit transient, C-1 Meisenheimer adduct (Scheme 5).[58,60b,118,119] The mechanism advanced for methanolysis of 1-halo-2,4-dinitrobenzenes with methoxide in methanolic DMSO also invokes either C-5 or C-3 adducts, as well as the necessary C-1 regioisomer.[120] In the reaction of sulfite ion with 1-chloro-2,4-dinitrobenzene the initial adduct formed has been definitively assigned by Bunnett, Gisler, and Zollinger[121] to the C-5 regioisomeric adduct, and neither C-3 nor C-1 adducts were observed, although eventual formation of the 2,4-dinitrobenzenesulfonate ion (under phase-transfer catalytic conditions) likely occurs via the metastable

Scheme 5



C-1 adduct. In the 2,4-dinitroanisole–MeO^- system[61g,122] and the 2,4-dinitrophenyl ethyl ether–ethoxide and –methoxide systems,[122,123] the initial adducts identified *at ambient or higher temperatures (i.e.* 37 °C*)*[124] were the C-1 adducts. However, the requirement for low-temperature NMR observation to detect the OH^- adduct of 1-chloro-2,4-dinitrobenzene recently[60b] suggests that C-5 (or C-3) adduct formation may be kinetically favored, but that these complexes had already isomerized to the thermodynamically more stable C-1 regioisomers at the time and temperature of observation.[61g,122,123] In an extreme example, ^{1}H NMR observation of the reaction of OH^- with the 2,4-dinitrophenyl ether of poly(ethylene glycol) (DNPEG) led to detection only of the C-1 PEG–alkoxide ($PEGO^-$) adduct of the ether (C-1 DNPEG·$OPEG^-$). Apparently attack of OH^- (ultimately at C-1) with rapid displacement of $PEGO^-$ results in attack of $PEGO^-$ on C-1 of the remaining substrate which yields the only observable adduct: C-1 DNPEG·$OPEG^-$. Otherwise the initial room temperature spectrum only contained the product 2,4-dinitrophenoxide ion.[42b]

Proceeding to monoactivated electrophiles, assignment of regioselectivity in mononitroarene systems is hampered by the fact that the relevant regioisomeric Meisenheimer complexes are generally not observed.[35,36] Analysis based on product studies is also difficult. Recall that in the study of the competition between VNS and S_NAr displacement in the 1-fluoro-4-nitrobenzene system, the yield of VNS products was directly tied to the amount of added base in the reaction.[38b] With these provisos, it would still appear that for 1-X-4-nitrobenzenes O-nucleophiles preferentially form products by displacement

of leaving groups *para* to the activating nitro group,[4] whereas suitably substituted C-nucleophiles, as in the VNS reaction,[7,38] form products primarily from attack at a position *ortho* to the nitro group and *meta* to X.

Although the current review has focused on those aromatic systems in which traditional electron-withdrawing groups (i.e. CN, SO_2CF_3, and particularly, NO_2)[4] activate aromatic rings to nucleophilic attack, it should be pointed out that the S_NAr mechanism also applies with less conventional electron-withdrawing activators. For example, phenylazo[125a] and pyridylazo[125b] groups become significant electron acceptors, which activate (monosubstituted) alkyl aryl ethers such as 4-(*p'*-sulfophenylazo)-1-naphthyl methyl ether[125c] and 4-[(*p'*-methoxyphenyl)azo]pyridine to S_NAr displacement by water, in mildly to moderately acidic media. Thus, 4-[(*p'*-methoxyphenyl)azo]pyridine has been shown by Buncel and Onyido[125b] to react via an A-2 mechanism in which the rate-determining step is actually S_NAr addition of water to the substrate at the methoxyl position, *para* to the diprotonated pyridylazo group. More recent studies of these alkyl aryl ether systems correlate the type of mechanism with the position of the leaving alkoxyl group relative to the activating protonated azo function.[125d] Another interesting electron-withdrawing group for monoactivated benzenes is the 6-azulenyl substituent examined by Bolton and co-workers.[126] Here activation to nucleophilic attack is the result of dipolar resonance forms in the azulenyl moiety.[126c,d]

Drawing upon the observations given above and those compiled in Table 1, we can make the following tentative generalizations. First, localized O-nucleophiles (e.g. OH^- and RO^-) react at unsubstituted sites initially, followed by rearrangement to the thermodynamically preferred adduct. This is the general K3T1 regioselectivity found in picryl ether–RO^- systems,[61a-g,62,85,98,127] which extends to the 7-halo-4-nitrobenzofurazan and 7-methoxy-4-nitrobenzofuroxan reactions with alkoxide(s) (as K5T7)[112,113] and which likely also applies to the 2,4-dinitrophenyl ether–RO^- and $-OH^-$ systems with modification to account for the two different unsubstituted sites (C-5, C-3) of potential reaction.[60b,61g,118,123] Delocalized (and more polarizable) O-nucleophiles such as PhO^- and 2,4,6-trimethylphenoxide (mesitoxide, $MesO^-$), on the other hand, follow either the K1T1 (K7T7)[88] pattern (e.g. TNA–PhO^- system)[85] or K1T3 regioselectivity (e.g. TNA–$MesO^-$ system).[87]

Secondly, carbon-centered nucleophiles, almost all of which are delocalized[7,84] (i.e. PhO^-,[85] $-CH_2COCH_3$,[61g] ^-CLYZ,[7] etc.) form C-3 adducts, or comparable adducts from attack at unsubstituted ring positions, as the kinetically favored products. On the basis of the calculated thermodynamic stability of the C-3 TNA·CH_3^- adduct relative to its C-1 counterpart[93] these nitroarene–C-nucleophile systems exemplify K3T3 regioselectivity (Figure 1). This generalization is consistent with the body of observations made by Makosza and co-workers on the regioselectivity of product formation in those systems where S_NAr displacement and VNS could compete.[7,38a,b] At first glance, CN^- appears anomalous. With TNA it reacts according to K1T3 regioselectivity,[63] whereas with TNT the K3T3 pattern prevails,[83] as with other C-nucleophiles. This apparent anomaly will be discussed further below.

Finally, there are a number of examples of N-nucleophiles which react with activated aromatics according to the K1T1 pattern of behavior, including the reactions of N_3^-,[64] *n*-butylamine,[65] and *tert*-butylamine[101] with TNA and *n*-propylamine with picryl–PEG.[41] On the other hand, Crampton and co-workers have investigated the reactions of ethyl 2,4,6-trinitrophenyl ether with *n*-butylamine, pyrrolidine, and piperidine by fast kinetic techniques and determined the regioselectivity as K3T1.[68] It is difficult to reconcile these results. Clearly, one possibility is that the K1T1 systems are actually only "pseudo-K1T1"; rearrangement of an initial C-3 adduct to its C-1 counterpart could have occurred prior to the moment of first observation (*cf.* Figure 1, dotted line portion of K3T1 profile). Further analysis of amine systems (and likely other systems involving neutral protic nucleophiles such as thiols) must await compilation of fast kinetic data for those systems in which initial nucleophilic attack on the electron-deficient substrates is rate determining.

It is apparent that the regioselectivity in many systems is strongly tied to the nature of the nucleophile, as well as the electrophile, and the rich diversity of behavior suggests a fine balance in the energetics of formation of the regioisomeric adducts.

5. Energetics of C-1 and C-3 O-Adduct Formation with TNA. How Do the Patterns of Regioselectivity Metamorphose? (K3T1 → K1T1 → K1T3)

The reactions of TNA with O-centered nucleophiles almost span the gamut of possible regioselectivity—from K3T1 in the TNA–MeO^- system, to K1T1 with PhO^- acting as an O-nucleophile, and finally to K1T3 behavior in the TNA–$MesO^-$ reaction system.[62,85,88,89] Consequently, it is useful to focus on the energetics involved in these three systems. Specifically, what changes in energetics cause a picryl-ether-nucleophile system to become transformed from K3T1 to K1T1 or from K3T1 to K1T3?

In order to obtain estimates of the energetics and so assess what changes in kinetics and stability account for the interconversion in regioselectivity, certain assumptions should be justified. In Table 1 and throughout this article systems that differ in terms of solvent used in the various studies have been presumed to be approximately equivalent. In this particular comparison the data available concerning the C-1 and C-3 TNA·OMe^- adducts (**9** and **10**, respectively) were determined in DMSO/MeOH, in a region rich in methanol.[36d] In fact, the majority of data in the literature concerning rates and equilibria for formation of Meisenheimer adducts have been measured in alkoxide–alcohol media or in a solvent medium of the alcohol and DMSO.[35,36] On the other hand, NMR studies have generally been made using media rich in DMSO, at least partly because of the well-known ability of DMSO to enhance Meisenheimer complex formation.[86] However,

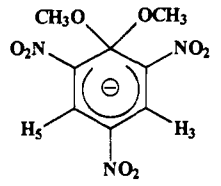
Table 2. Comparison of Rate and Equilibrium Data for the TNA O-adducts, 9–12[a]

adduct	k_1 (s^{-1})	k_{-1} (s^{-1})	$\Delta G_1^{\ddagger}$ (kcal/mol)[b]	$\Delta G_{-1}^{\ddagger}$ (kcal/mol)[b]	K (M^{-1})	ΔG_1° (kcal/mol)[c]
C-1 MeO^-, **9**	4.3×10^3	2.4×10^{-6}	12.5	25.1	1.8×10^9	−12.6
C-3 MeO^-, **10**	1.8×10^5 [e]	2.6×10^{-1} [e]	10.3	18.3	7.0×10^5	−8.0
C-1 PhO^-, **11**	5.0×10^4	1.75×10^2	11.2	14.6	2.85×10^2	−3.4
C-1 $MesO^-$, **12**[d]	2.6×10^4	3.0×10^2	11.6	14.3	8.7×10^1	−2.7

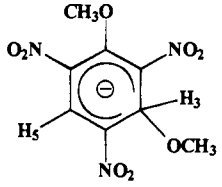
[a] Estimates for **12** refer to DMSO/H_2O 90:10 v/v at 30 °C[89] while those for **9** and **10** were determined from data in ref 36d, extrapolated to DMSO/MeOH 80:20 v/v at 25 °C (log k vs mol fraction DMSO plots), using density data of Bicknell *et al.* (ref 126) to make conversions from volume % to molar fraction. Both solvent systems comprise 0.696 mol fraction DMSO. Data for 11 taken from ref 89 and refer to DMSO/H_2O 90:10 v/v at 30 °C. [b] Calculated from the Eyring equation, *cf.* Bunnett, J. F. In *Techniques in Organic Chemistry*; Wiessberger, A., Ed.; Interscience: New York, 1961; Vol. VIII, Part 1, p 200, eq 11. [c] Calculated from $\Delta G^{\circ} = -RT \ln K$. [d] Interpolated from the Brønsted line for substituted phenoxides reacting at C-1 of TNA, ref 89. The pK_a value for mesitol (15.16) was extrapolated to 0.696 mol fraction DMSO using the data of ref 125. [e] $k_1 = k_3$, $k_{-1} = k_{-3}$ for this adduct; Scheme 1.

it is possible to extrapolate kinetic and equilibrium data to a relatively high DMSO concentration, even though straight-line correlations are likely fortuitous.[36d]

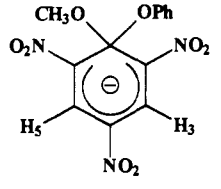
A more serious consideration in the present comparison arises from the fact that the NMR studies of the TNA–PhO^- and TNA–$MesO^-$ systems, wherein the O-adducts were detected and their fate monitored, were undertaken in the novel medium, acetonitrile/glyme (1:1 v/v). This solvent mixture has the advantage of being fluid to temperatures as low as −50 °C and it has proven to be very useful in these studies, as a result.[85,87,88,90a] However, recently we showed that this solvent mixture has bulk properties reasonably similar to those of DMSO or DMSO/ROH media.[87] Therefore, the data compiled in Table 2 for formation of the adducts **9** and **10** and the C-1 TNA O-adducts with PhO^- (**11**) and with $MesO^-$ (**12**), determined[89,124] or estimated[87] in 0.696 mol fraction DMSO media, in fact, are valid approximations for the values that would obtain in MeCN/glyme (1:1).



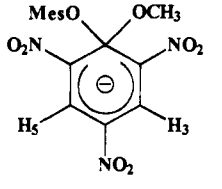
9



10



11



12

Differences in solvent in these (or other systems that have been classified in Table 1) will likely affect the absolute magnitudes of the values for the rates and equilibrium constants but may not disrupt the trends found.

In comparing the TNA aryloxide O-adducts with the C-1 TNA·OMe^- adduct, **9**, it is striking that the aryloxide adducts, **11** and **12**, are both so unstable relative to **9**. Thus, the C-1 TNA·OMe^- adduct, **9**, is more stable than the C-1 TNA·OPh^- adduct, **11**, by 9.2 kcal/mol [$\Delta\Delta G^{\circ}$(**9**–**11**) = −9.2 kcal/mol],while **9** is favored over **12** by 9.9 kcal/mol [$\Delta\Delta G^{\circ}$(**9**–**12**) = −9.9 kcal/mol]. Moreover, both C-1 aryloxide adducts are even less stable than the C-3 TNA·OMe^- adduct, **10** [$\Delta\Delta G^{\circ}$(**10**–**11**) = −4.6 kcal/mol and $\Delta\Delta G^{\circ}$(**10**–**12**) = −5.3 kcal/mol].

These energetics are clearly consistent with the K1T3 regioselectivity found in the TNA–$MesO^-$ system where **12** is formed under kinetic control but gives way to the thermodynamically more stable C-3 O-adduct. After all, **12** is a relatively unstable adduct and, hence, transient. However, the TNA–PhO^- system displays K1T1 regioselectivity even though the C-1 TNA·OPh^- adduct, **11**, is also unstable relative to the C-1 TNA·OMe^- adduct, **9**. Importantly, **11** is more stable than **12** albeit by only 0.7 kcal/mol. Is this degree of stabilization of **11** (relative to **12**) enough to account for the change in regioselectivity (K1T1 to K1T3)? The answer clearly depends upon the relative stabilization of the corresponding C-3 adducts: TNA·$OMes^-$ and TNA·OPh^-.

The relative magnitudes of the standard free energies for formation of the C-1 adducts can be placed in perspective by first considering the free energies of activation. In this regard, the difference in the formation activation barrier between **9** and **11** is only 1.3 kcal/mol and between **9** and **12** only 0.9 kcal/mol ($\Delta\Delta G_1^{\ddagger}$) favoring formation of **11** and **12**, respectively, over **9**. As required by the classification of regioselectivity, attack at C-1 of TNA by PhO^- or $MesO^-$ appears to be kinetically favored (i.e. the K1 in K1T1 and K1T3). It is noteworthy that the kinetics in these systems are finely balanced. The $\Delta G_1^{\ddagger}$ for formation of the C-3 TNA·OMe^- adduct, **10**, is only 0.9 kcal/mol lower than that for formation of **11** and only 1.3 kcal/mol lower than the activation energy for formation of **12**. At the same time, the forward activation energies for formation of the C-3 adduct, **10**, and its C-1 MeO^- counterpart, **9**, differ by a relatively small 2.2 kcal/mol. Therefore, small changes in the nucleophile can cause considerable modification of rate and equilibrium constants and, hence, can have profound effects on the pattern of behavior of these picryl ether–nucleophile systems, as detailed in Table 1.

The differences in adduct stability ($\Delta\Delta G^{\circ}$) arise primarily from differences in ease of decomposition of the adducts back to starting electrophile and nucleophiles. Thus, $\Delta\Delta G_{-1}^{\ddagger} = 10.5$ kcal/mol between **9** and **11** and 10.8 kcal/mol between **9** and **12**. The obvious ease of decomposition of **11** and **12**, as compared to **9**, no doubt is partly attributable to the greater nucleofugality of phenoxide and mesitoxide as compared to methoxide (*cf.* pK_a of phenol and

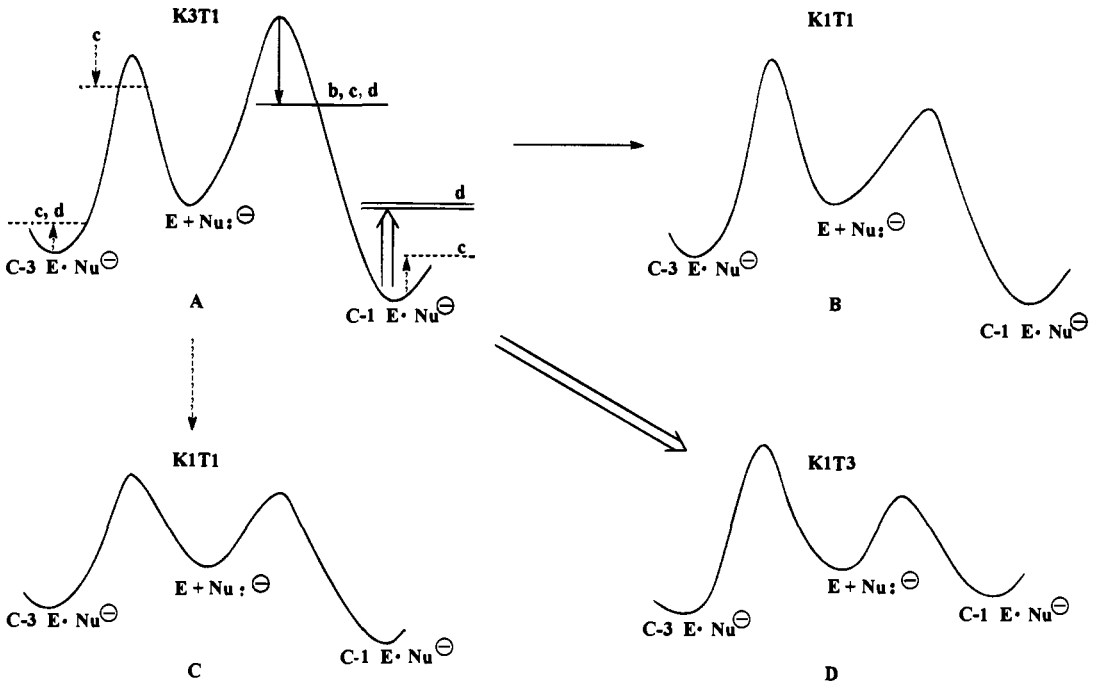


Figure 2. In **A** the qualitative energy profile for K3T1 regioselectivity is reproduced. The **solid arrow** from **A** to **B** also indicates the decline in the k_1 kinetic barrier (**solid arrow** from the transition state for formation of the C-1 adduct to the new lower energy transition state at the line labeled **b**, **c**, **d**); this is the *minimum* change needed to convert K3T1 regioselectivity (**A**) into the K1T1 profile (**B**). The energetics (Table 2) suggest that for the TNA–PhO^- system the changes in kinetics and thermodynamics indicated by the **dashed arrows** labeled **c** actually occur to metamorphose K3T1 into the K1T1 profile **C**. The further change in the relative stability of the C-1 adduct in the TNA–$MesO^-$ system shown by the **open arrow** and labeled **d** is required to account for the transformation of K3T1 behavior into K1T3 behavior shown in **D**.

mesitol vs that of methanol).[124,129] In the case of mesitoxide, steric congestion also accelerates the breakdown of the C-1 TNA·$OMes^-$ adduct, **12**. Note, however, that when the nucleophile is "held constant" as in the case of the TNA·OMe^- adducts, **9** and **10**, there is also an appreciable activation free energy difference of 6.8 kcal/mol in favor of the decomposition of the C-3 adduct, **10**.

Although there are no numerical values available for the energetics involved in formation of the TNA·OPh^- or TNA·$OMes^-$ adducts, it has generally been found useful to consider a C-3 adduct of a picryl ether as being similar to a TNB adduct with the same nucleophile.[35] In fact, the TNB adduct with hydroxide has very similar stability to the C-3 TNA·OH^- adduct, according to recent AM1 calculations.[93] It is significant, then, that while both TNB·OPh^- and TNB·$OMes^-$ adducts have recently been unambiguously identified and characterized in the MeCN/glyme solvent system[90a] *at low-temperature*, detection of such adducts at room temperature in DMSO has been fraught with difficulties to the point where it is unlikely that these aryloxide O-adducts can be observed at ambient temperature. On the other hand, alkoxide adducts of TNB are readily observed in DMSO/ROH media at room temperature,[35] which suggests that C-3 aryloxide adducts of TNA would be significantly less stable than their alkoxide analogs, even though detectable if formed using the low temperature, MeCN/glyme conditions. Furthermore, the same higher nucleofugality expected for the aryloxides as compared to methoxide that partly accounts for the reduced stability of **11** and **12** as compared to **9** should also operate in the corresponding C-3 adducts; the C-3 TNA·OPh^- and TNA·$OMes^-$ adducts should break down more facilely than the C-3 TNA·OMe^- adduct, **10**, and the C-3 aryloxide adducts should be less stable than **10**.

Inherent in the estimation of the energetics for the C-1 TNA·$OMes^-$ adduct, **12**, was the requirement that values of the forward and reverse rate constants for attack at C-1 (k_1 and k_{-1}) be interpolated from the Brønsted plots of pK_a of phenols (*para*-substituted phenoxide O-nucleophiles) vs log k_1 and log k_{-1}, as determined by Bernasconi and Muller[89] for the O-adducts of TNA. On steric grounds it could well be argued that mesitol would deviate from these two Brønsted correlation lines and so the estimated value of k_1 should be viewed as an upper limit and the predicted k_{-1} value (Table 2) constitutes a lower limit. In combination, the C-1 TNA·$OMes^-$ adduct would then be less stable than Table 2 suggests and the relative stability of the C-1 TNA·OPh^- adduct, **11**, would be accordingly greater.

How does the K3T1 profile (TNA–MeO^- system) slide over to K1T1 (TNA–PhO^- system)? It is tempting to point out the significant decline in the activation barrier for formation of the C-1 TNA·OPh^- adduct, **11**, as compared to the C-1 TNA·OMe^- adduct, **10** and attribute the transformation to this alone (Figure 2A → 2B). In fact, such a reduction in this single C-1 barrier could account for a change in regioselectivity (K3T1 → K1T1) in a system such as the picryl fluoride–F^- system.[110] Fluorine has a smaller atomic radius than hydrogen and, therefore, attack at the "substituted" position of picryl fluoride would involve *less* F strain[98,130] than attack at the unsubstituted C-3 site. Nonetheless, the energetics determined for the TNA–ArO^- systems are more complex (Table 2). These energetics demonstrate

that while the barrier to attack at C-1 declines such that k_1 is now greater than k_3 there is also an increase in k_{-1} so that K_1, the equilibrium constant for formation of the C-1 phenoxide O-adduct, **11**, declines. This is apparently compensated for by a reduction in the magnitude of K_3, the equilibrium constant for formation of the C-3 phenoxide adduct, consistent with the greater leaving group ability of PhO^- as compared to MeO^-. Therefore, while k_1 increases so that $k_1 > k_3$ and k_{-1} also increases, K_1 remains greater than K_3, and the regioselectivity is transformed into K1T1 (Figure 2C).

In the case of the TNA–$MesO^-$ system, k_1 for attack at C-1 increases relative to the value of k_1 for attack at C-1 attack by MeO^-, although not to as great a degree as the increase in k_1 for PhO^- as compared to MeO^-, partly owing to the greater F strain[85,130,131] involved in attack of the bulky $MesO^-$. However, steric acceleration to decomposition, as well as other steric factors affecting C-1 adduct stability (see below), result in a larger k_{-1} value for breakdown of the C-1 TNA·$OMes^-$ adduct, **12**. While K_1 declines, therefore, the magnitude of k_3 does not fall to the same degree, k_3 is now greater than k_1 and the profile metamorphoses from K3T1 into K1T3, the inverse regioselectivity (Figure 2D) to the K3T1 regioselectivity commonly found in TNA–alkoxide systems.

The importance of the change in thermodynamic stability of the aryloxide adducts as compared to the methoxide adducts (Table 1) overshadows the individual kinetic effects. Thus, in focusing on the observation that K3T1 transforms into K1T1 regioselectivity not by a slight modification of a single kinetic barrier (Figure 2B) but by a more convoluted sequence of changes involving the thermodynamics of all of the adducts (Figure 2C) the question arises: What factors account for the destabilization of the C-1 TNA·OAr^- adducts relative to their TNA·OMe^- counterparts?

6. Factors Affecting Regioselectivity: The Importance of Stereoelectronic Stabilization in C-1 Adducts

Possible origins of kinetic and thermodynamic preferences in C-1 vs those in C-3 attack on picryl ethers and related compounds have been discussed by a number of workers.[4] These factors include F strain to attack[98,128,129] which may be mitigated by the polarizability of the attacking nucleophile (in a hard–soft acid–base sense)[85,132,133] stabilization of C-3 adducts (and/or transition states leading to C-3 adducts) by charge-separated canonical forms,[61e,f] ion pairing that could stabilize C-1 dialkoxy adducts,[98,134] and relief of steric congestion at C-1 that accompanies formation of C-1 adducts but not C-3 adducts.[130,135] It has also been long recognized that geminal dialkoxy substitution carries with it enhanced stabilization for such C-1 adducts.[136,137]

While the mechanism of action of geminal disubstitution of electronegative groups at C-1 in stabilizing a C-1 adduct was linked to anionic hyperconjugation[138] it has more recently been described in molecular orbital terms[139] and with relevant comparison of C-1 dialkoxy Meisenheimer adducts, such as **9**, to acetals.[73,140,141] In our studies of the TNA–aryloxide systems[85,87,88] we have highlighted the significance of this stereoelectronic stabilization in assessing the pattern of regioselectivity that will obtain and more recently the importance of such stabilization has emerged from our AM1 calculations on Meisenheimer complexes.[93]

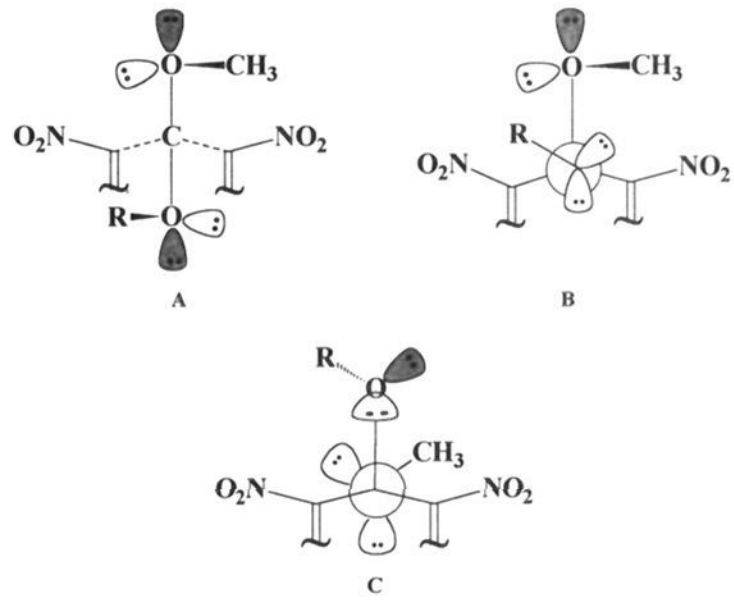


Figure 3. Rotameric forms of the C-1 TNA·OR^- adducts, showing the antiperiplanar arrangement of the RO lone pair to the C–OCH_3 bond and the comparable antiperiplanar placement of the CH_3O lone pair relative to the C–OR bond. This doubly antiperiplanar arrangement maximizes the n–σ^* interaction. View **A** is taken from above the RO–C(1)–OCH_3 axis, while the Newman rojection **B** is obtained by sighting down the RO–C(1) bond and **C** by sighting from C(1) to the OCH_3 group along the bond. Note that other rotamers also place the relevant lone pairs and bonds antiperiplanar, including the enantiomers of the structures shown here.

Ideally, C-1 dialkoxy adducts, as analogs of acetals, can be stabilized by donation of lone pair electron density from one C-1 alkoxyl oxygen to the σ^* orbital of the antiperiplanar C–OR bond and vice versa. In symmetrical C-1 adducts, such as the C-1 TNA·OMe^- adduct, **9**, maximum stereoelectronic stabilization would result from the antiperiplanar arrangement of each C–OR bond relative to a given lone pair of the other geminal OR group. This "doubly antiperiplanar" arrangement is shown in Figure 3, using sp^3 hybrid orbitals for the oxygen lone pairs with the omission of the minor lobes for the sake of clarity.[139a] While such a doubly antiperiplanar arrangement would maximize n–σ^* stabilization of the C-1 adduct we recognize that steric interactions between the geminal alkoxyls and the adjacent nitro groups of the cyclohexadienate ring could restrict access to the ideal rotameric forms[85] and, so, stereoelectronic stabilization could be less than optimum even in a symmetrical TNA·OR^- C-1 adduct.[93]

In unsymmetrical C-1 adducts, such as the C-1 TNA·OPh^- and C-1 TNA·$OMes^-$ adducts, another factor must be considered. Even if suitable doubly antiperiplanar conformers are readily accessible through rotation and even if such forms would be expected to be populated at a given temperature, the efficacy of the n–σ^* stabilization will depend on the relative energies of the two σ^* fragment orbitals. Thus, n donation from OPh in adduct **11** to the σ^* orbital of the OCH_3 fragment may be more or less effective than n donation from OCH_3 to the σ^* orbital of OPh. In general, then, unsymmetrical C-1 adducts

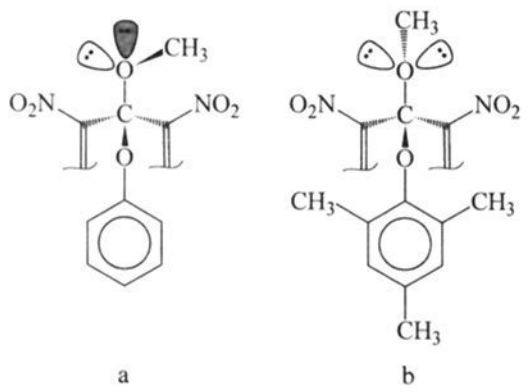


Figure 4. (a) Illustration of stereoelectronic stabilization of the C-1 phenoxide O-adduct (C-1 TNA·OPh$^-$, **11**) through a single antiperiplanar interaction between the lone pair on the methoxyl oxygen and the C−OPh bond. (b) Illustration of the C-1 TNA·OMes$^-$ adduct, **12**, where stereoelectronic stabilization is not possible.

should exhibit less stereoelectronic stabilization than their symmetrical counterparts, regardless of whether their most favorable rotameric forms are accessible or not. In this context, such diminished n−σ* stabilization of unsymmetrical C-1 adducts is likely a factor in the facile amine exchange reactions reported by Sekiguchi and co-workers for picryl, 2,4-dinitronaphthyl, and 2,4-dinitrophenyl amines,[142] and in the alkaline hydrolytic deamination of similar electron-deficient aryl amines studied by De Rossi and De Vargas.[143]

In the series of C-1 O-adducts, TNA·OMe$^-$, **9**, TNA·OPh$^-$, **11**, and TNA·OMes$^-$, **12**, inferences drawn from models (Darling or Fieser), as well as ^{13}C NMR spectroscopic evidence,[87] suggested that while maximum stereoelectronic stabilization would be possible for **9**, it was likely that a lower degree of stabilization would accrue to **11**, not just because it is an unsymmetrical adduct but as a result of steric factors and possible lone pair−aryl π-cloud repulsion that would make the doubly antiperiplanar rotameric forms inaccessible. However, for **11**, forms that permit stereoelectronic stabilization with a single n−σ* interaction would be significantly populated along the rotameric continuum. Note that this inference is consistent with the energetic information; **9** *is* thermodynamically more stable than **11** (Table 2). Moreover, steric hindrance would be so great in TNA·OMes$^-$ that no stereoelectronic stabilization could be expected for this C-1 adduct.

Figure 4 illustrates the type of single antiperiplanar arrangement that would be expected to be populated for the C-1 TNA·OPh$^-$ adduct and, so, stabilize it, as well as the rotameric form that likely predominates for the C-1 TNA·OMes$^-$ adduct, **12**. The conclusion is that the trend in the stereoelectronic stabilization of the C-1 adduct corresponds to the thermodynamics of the regioselectivity found in the three TNA reaction systems; **9** is strongly stabilized by the stereoelectronic interaction and in the TNA−MeO$^-$ system the C-3 adduct, **10**, rearranges to this more stable C-1 adduct, displaying K3T1 regioselectivity (Figure 1). In the TNA−OPh$^-$ system, **11** is much reduced in thermodynamic stability (relative to **9**) but is still more stable than its C-3 counterpart and the system shows K1T1 behavior, but in the TNA−OMes$^-$ system the C-1 adduct is so destabilized that it readily rearranges to its C-3 regioisomer in K1T3 regioselectivity.

The facile decomposition of the C-1 TNA·OMes$^-$ adduct, **12**, is clearly a function of steric hindrance and there is no doubt that steric hindrance is important to determining the regioselectivity in picryl ether nucleophile systems in a number of ways. While F strain to attack has been previously invoked[98,130,131] along with relief of steric strain at the C-1 position upon formation of the C-1 adduct (i.e. as the C-1 sp^2-hybridized center is converted into an sp^3-hybridized center in the C-1 adduct),[130,131,135] it is now apparent that steric hindrance can also function by "shutting down" the stereoelectronic stabilization in a C-1 adduct. In fact, it is reasonable to think that there is an interplay between the various steric factors in these systems. Steric hindrance to C-1 attack in the TNA−MesO$^-$ system, for example, may be compensated for by stabilization of the transition state for C-1 adduct formation by the partial relief of strain that occurs in the transition state.[85,87] Once the C-1 adduct is formed, however, steric factors prevent its stereoelectronic stabilization and accelerate its decomposition.

Similar synergistic effects may occur in other systems where adducts may be formed that are geminally disubstituted with electronegative groups. For example, the picryl fluoride−F$^-$ system shows K1T1 regioselectivity.[110] F strain to attack at the C-1 position is actually lower than F strain to attack at C-3. This accounts for the K1 part of K1T1 and the stereoelectronic stabilization that would be expected for the C-1 picryl fluoride·F$^-$ adduct provides the T1 in K1T1. Similar arguments may be applied to the TNA·N_3^- system that shows K1T1 regioselectivity.[64]

It should be pointed out that we have only considered n−σ* stabilization as a thermodynamic factor. No doubt F strain, the effect of charge-separated canonical forms on the transition state for C-3 adduct formation and the effect of relief of C-1 strain in the transition state leading to C-1 adduct formation are significant factors that account for the kinetic preferences found in these systems (Table 1).

Most recently we reported the results of AM1 calculations on the enthalpy of complexation for formation of a series of regioisomeric adducts of methide, methoxides and hydroxide anions with a range of electron-deficient aromatics.[93] The study supported the view that stereoelectronic stabilization constitutes a significant thermodynamic factor in determining regioselectivity. Therefore, reaction of a series of increasingly electron-deficient substrates, namely, nitrobenzene, 1,3-dinitrobenzene, and TNB, leads to formation of regioisomeric Meisenheimer adducts. In the calculation study, hydroxide and methide anions served as the model oxygen and carbon nucleophiles. The calculations show that the same regioisomeric adducts of both OH$^-$ and CH_3^- are formed with the greatest exothermicity (ΔH_c) and, so, show the same thermodynamics of regioselectivity. The ΔH_c was derived from eq 7, using the AM1 calculated heats of formation (ΔH_f), except for the highly localized nucleophiles where gas-phase experimental ΔH_f values were used, thus

$$\Delta H_c = \Delta H_f(\text{E}\cdot\text{Nu}^- - [\Delta H_f(\text{E}) + \Delta H_f(\text{Nu:}^-)]) \quad (7)$$

where E represents the aromatic electrophile, Nu:$^-$

is OH^- or CH_3^- (or CH_3O^-) and E·Nu^- identifies the resultant Meisenheimer adduct. In the case of this series, adducts formed as a result of attack at a position *para* to at least one nitro group are formed with the greatest exothermicity (ΔH_c).

However, with 1-fluoro-4-nitrobenzene and with TNA there is an inversion of behavior for CH_3^- as compared to OH^- (or CH_3O^- in the reaction with TNA). Now the greatest exothermicity results from attack at the substituted C-1 of 1-fluoro-4-nitrobenzene for OH^-, but at the unsubstituted position *ortho* to the nitro group for CH_3^-. For the TNA systems CH_3O^- and OH^- form their most stable adducts at C-1, but the C-3 adduct TNA·CH_3^- is formed with *slightly* greater exothermicity than its C-1 analog. These results are consistent with the expected degree of stereoelectronic stabilization in the respective C-1 complexes. In both systems the O-nucleophiles can act as n electron donors and the C−OR (C−OH) bonds formed in these C-1 adducts can act as σ^* acceptors. Although in the case of OH^- attack the C-1 adducts would be unsymmetrical and be expected to have somewhat decreased stereoelectronic stabilization relative to symmetrical adducts, the exothermicity of their formation does correlate with a degree of n−σ^* stabilization. The CH_3^- adducts, on the other hand, cannot partake of such stabilization since no lone pairs are present on the bonded CH_3 fragment. As well, the C−CH_3 bond would be less efficient as an acceptor than the O−CH_3 bond because of the comparatively high n−σ^* energy gap.[139,144] Consequently, the C-3 TNA·CH_3^- adduct is thermodynamically preferred over its C-1 counterpart.

A similar argument may extend to the TNA−CN^- system.[63] Here the linear ion, CN^-, would encounter reduced F strain to attack at C-1 to the extent that such attack could be kinetically favored. Thermodynamically, the C-1 TNA·CN^- adduct could be destabilized relative to its C-3 regioisomer because of the lack of effective n−σ^* stabilization. In combination, the system would slide over to K1T3 regioselectivity.[63] The behavior of cyanide ion is consistent with that found in the von Richter reaction.[2b,4] Attack of CN^- occurs competitively at substituted and unsubstituted sites of 1-X-mononitrobenzenes, but rearrangement with cine substitution follows as irreversible processes after attack at the unsubstituted site *ortho* to the nitro group. Clearly, cyanide, as a C-nucleophile, demonstrates its thermodynamic preference for attack at an unsubstituted position *ortho* to (at least) one NO_2, as previously noted in the VNS reaction involving other C-nucleophiles.[7,38]

On the other hand, recent results obtained from the reaction of methoxide in MeOH with 7-methyl-4-nitrobenzofuroxan emphasize the fine balance between kinetics and thermodynamics in these systems.[145] In this case, the adduct initially detected by stopped-flow spectrophotometry is the C-5 methoxy adduct from attack of MeO^- at C-5 (*ortho* to the 4-nitro group and *meta* to the 7-methyl group of the substrate); this C-5 adduct rearranges to the more stable C-7 adduct in K5T7 behavior outlined above for other systems.[112,113] Apparently, the diminished stereoelectronic stabilization available to the C-7 adduct in this system, as well as any steric hindrance to C-7 attack, are offset by other factors, possibly including improved delocalization of charge into the furoxan ring in the C-7 adduct.[145] It is also germane to this discussion to note that analogous K3T1 behavior, as well as K3T3 regioselectivity, has been found in the related 2,4,6-trinitrotoluene (TNT)−alkoxide systems and that competitive benzylic proton abstraction plays a role in these systems that it apparently does not in the heterocyclic system.[81,105-108]

Where stereoelectronic stabilization is impossible, as in the adducts formed by nitrobenzene, 1,3-dinitrobenzene, and TNB, the AM1 calculations[93] show that OH^- and CH_3^- would display the same regioselectivity, as far as exothermicity of adduct formation can predict.

Interestingly, the calculations performed on the C-1 TNA·OMe^- adduct yielded two minimum energy structures after optimization of the geometry.[93] In the presence of a point charge that simulates an ion-paired cation, an "M-shaped" conformer is energetically favored for the C-1 adduct, while in the absence of this charge an "S-shaped" conformer is favored. Without a complexing "fake ion" M and S conformers are both local minima, while the S conformer constitutes the global minimum.

The M conformer is calculated to be 4.4 kcal/mol less stable ($\Delta\Delta H_c$) than the S conformer, which places one methyl group over the trinitrocyclohexadienate ring. When the simulated cation complexes to the geminal methoxyls and adjacent nitro groups it induces the M conformer, locks the methoxyl groups in place, inhibits rotation, and therefore, prevents the methoxyls from achieving conformations that permit n−σ^* interaction. Importantly, in the S conformer neither lone pair of either acetal-like oxygen is placed in the optimal antiperiplanar position (*cf.* Figures 3 and 4a) but there is the possibility of partial interaction of both lone pairs with the relevant C−O acceptor bond. It is noteworthy that Bernasconi and Howard[140] had deduced the dominant rotameric form of this C-1 adduct in solution, in the absence of complexing counterions (in methanol), from an analysis of the kinetics of spiro Meisenheimer adduct formation and ring-opening decomposition.

The salient point is that in the S-shaped rotamer a trade is made: n−σ^* stabilization for minimization of steric hindrance between the groups at C-1 and between these groups and the nitro groups of the trinitrocyclohexadienate ring (Figure 5). It may be estimated that the stabilization in the S conformer is approximately equal to that provided by a single antiperiplanar interaction (Figure 4a) and this would suggest that in the TNA·OPh^- C-1 adduct, **11**, the preferred conformation may also be intermediate between any of the maximum interaction forms (Figure 3). On the other hand, it is also likely that while the S form of the C-1 TNA·OMe^- adduct, **9**, is the energetically preferred rotameric form, other forms that provide greater degrees of n−σ^* stabilization are also appreciably populated in solution.

Nonetheless, the M and S conformations do aid in the explanation of the behavior of TNA−alkoxide systems upon addition of crown ethers. In the solid state, C-1 TNA·OR^- adducts are known to take up a

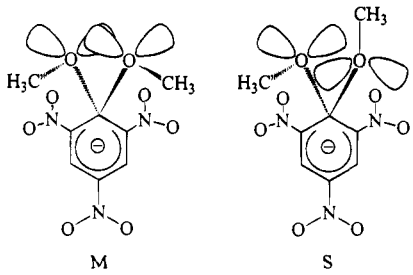


Figure 5. The conformational minima for the C-1 TNA·OMe⁻ adduct, **9**. The "S-shaped" conformer in which one methyl of the $CH_3O-C(1)-OCH_3$ moiety is pointed "down" and the other "up" and in which the lone pairs of the oxygens are staggered, is favored by 4.4 kcal/mol over the "M-shaped" conformer, according to AM1 calculations.[93] In the M confomer both methyl groups point down. The lone pairs of the oxygen of the "up" methoxyl in the S form can each participate partly in n–σ* stabilization, whereas the lone pairs of the oxygen of the "down" methoxyl cannot. Consequently, stereoelectronic stabilization is not possible in the M form. In this figure, the C(1)–O bond lengths are exaggerated and the minor lobes of the sp^3 hybridized lone pairs are omitted for clarity. Note that in both M and S forms the $CH_3O-C(1)-OCH_3$ moiety places the methyls in the same plane.

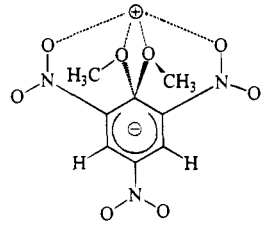


Figure 6. The C-1 TNA·OMe⁻ adduct, **9**, ion paired to a hypothetical counterion simulated by a point charge (AM1 calculation using the SPARKLE option). This structure is in accord with expected ion paired structures where the counterion is held in a "pseudo-crown ether" formed by the acetal-like geminal dimethoxyls and the adjacent oxygens of the nitro groups. The $C(2)-NO_2$ and $C(6)-NO_2$ bond lengths are exaggerated for clarity.

conformation similar to the M-shaped structure induced by the presence of the metal counterion (Figure 6).[146] In hydroxylic solvents (or DMSO/ROH cosolvents) Crampton and co-workers have found evidence for similar association of the counterion to the C-1 adducts.[88,134] Thus, the counterion is complexed to the geminal dimethoxyl oxygens and to the oxygens of the ortho nitro groups in a "pseudo-crown ether arrangement" in the C-1 TNA·OMe⁻ adduct, **9**, but the TNB·OMe⁻ adduct (a model for the C-3 TNA·OMe⁻ adduct, **10**) does not show this type of association of the cation with the adduct, which points out the essentiality of having both $O-CH_3$ groups present.[122,147] The complexation present in the M conformer provides stabilization that, in fact, exceeds that provided by n–σ* stabilization in the S conformer according to the AM1 calculations. Regardless, the C-1 adduct is still the product of thermodynamic control even when crown ethers are used to eliminate counterion complexation with the C-1 TNA·OMe⁻ adduct.

This is nicely explained by the presence of the two preferred conformers for the C-1 TNA·OMe⁻ adduct, namely M and S (Figure 5). In systems where ion pairing is dominant (e.g. in alcoholic solvents and where the counterion is relatively small like Na^+) the C-1 adduct is thermodynamically favored because of the stabilization conferred on the adduct by counterion complexation. However, in systems where this will not apply the C-1 TNA·OMe⁻ (and structurally similar adducts) will be the thermodynamic products because of the stereoelectronic stabilization afforded by conformers like S. In the absence of counterion complexation S is the more stable conformer.

7. Conclusions

In the S_NAr and VNS mechanisms of aromatic nucleophilc substitution the outcome of the reaction is partly dependent upon the regioselectivity shown by the nucleophile in formation of the intermediate Meisenheimer complex(es). This regioselectivity is the sum of kinetic and thermodynamic preferences for formation of the key Meisenheimer adduct intermediates. In fact, we have shown that for picryl ethers (and related compounds) a wide range of regioselectivity exists. The types of regioselectivity have been classified and the process whereby one pattern of regioselectivity (K3T1 in the TNA–MeO^- system, for example) is converted or metamorphoses into another pattern of regioselectivity (K1T1 in the TNA–PhO^- system) as a function of modifying the nature of the attacking nucleophile, has been delineated. The thermodynamics of this process arise from a number of factors of which stereoelectronic stabilization of the pertinent C-1 adduct, that is geminally disubstituted with electronegative groups, is particularly significant to the rationalization of the patterns of regioselectivity. Recent semiempirical (AM1) calculations support the analysis. Future work will likely extend the classification of regioselectivity to diactivated aromatic systems and to heteroaromatic electron-deficient substrates.

The types of regioselectivity that we have discussed for 1-X-2,4,6-trinitrobenzenes, primarily, also impinge on pratical considerations in many areas of chemistry that involve nucleophilic aromatic displacement. For example, in attempting displacements with carbon-centered nucleophiles the preference for attack at unsubstituted (*i.e.* C-3-like) positions should be taken advantage of. Exploitation of this regioselectivity is implicit in VNS reactions.[7,34,37,38] On the other hand, displacements at C-1 can be enhanced through the choice of leaving group, as well as nucleophile. Thus, a small leaving group, such as F, may be readily displaced by linear ions such as azide or cyanide,without the intervention of nonproductive adducts formed at unsubstituted positions. Such systems would be expected to show K1T1 behavior; kinetic preference because of lowered F strain to attack at C-1 (as compared to C-3) and thermodynamic preference due to stereoelectronic stabilization (however diminished it may be relative to that afforded the model C-1 TNA·OMe⁻ adduct).

Finally, it is our hope that the insights into regioselectivity outlined in this article will spur further research in the various areas considered in the Introduction—drug research, polymer synthesis, and environmental chemistry.

8. Acknowledgments

The authors sincerely thank the many graduate students and colleagues whose efforts in our and

associated laboratories have added much to the understanding of the systems discussed. This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada (NSERCC to E.B.), the Principal's Research Fund of Sir Wilfred Grenfell College (to J.M.D.), and the Centre National de la Recherche Scientifique (CNRS to F.T.).

References

(1) (a) Department of Chemistry, Queen's University, Kingston, Ontario, Canada, K7L 3N6. (b) Department of Chemistry, Sir Wilfred Grenfell College, Corner Brook, Newfoundland, Canada, A2H 6P9. (c) Université de Versailles, SIRCOB Bâtiment Lavoisier, 45 Avenue des Etats-Unis, Versailles Cedex 78035, France.

(2) (a) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 272. (b) Bunnett, J. F. *Q. Rev., London* **1958**, *12*, 15. (c) Bunnett, J. F. *J. Chem. Educ.* **1974**, *51*, 312. (d) Miller, J. *Nucleophilic Aromatic Substitution*; Elsevier: Amsterdam, 1968. (e) Buncel, E.; Norris, A. R.; Russell, K. E. *Q. Rev., London* **1968**, *22*, 123. (f) Buncel, E. *The Chemistry of Functional Groups. Supplement F. The Chemistry of Amino, Nitro and Nitroso Compounds*; Patai, S., Ed.; Wiley: London, 1982.

(3) Crampton, M. R. In *Organic Reaction Mechanisms 1991*; Knipe, A. C., Wattas, W. E., Eds.; Wiley: Chichester, 1993; Chapter 7, pp 229–242 and previous reviews in this series.

(4) Terrier, F. *Nucleophilic Aromatic Displacement. The Influence of The Nitro Group*; Feurer, H., Ed.; Organic Nitro Chem. Ser.; VCH: New York, 1991.

(5) (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (b) Bunnett, J. F. *Acc. Chem. Res.* **1992**, *25*, 2.

(6) Rossi, R. A.; De Rossi, R. H. *Aromatic Substitution by the S_{RN1} Mechanism*; ACS Monograph Ser. 178, American Chemistry Society: Washington, DC, 1983.

(7) (a) Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282. (b) Makosza, M. *Russ. Chem. Rev.* **1989**, *58*, 747. (c) Makosza, M.; Kinowski, A. *Bull. Pol. Acad. Sci. Chem.* **1989**, *37*, 127. (d) Makosza, M.; Daniekiewicz, W.; Wojciechowski, E. *Phosphorus Sulfur Silicon* **1990**, *53*, 457. (e) Makosza, M. *Pol. J. Chem.* **1992**, *66*, 3.

(8) Chupakhin, O. N. *Isv. Sib. Otd. Akad Nauk SSSR, Ser. Khim Nauk* **1990**, 110; *Chem. Abstr.* **1991**, *114*, 184514.

(9) Van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*, 462.

(10) (a) Van der Plas, H. C. *Tetrahedron* **1985**, *41*, 237. (b) Wozniak, M.; Van der Plas, H. C. *Acta Chem. Scand.* **1993**, *47*, 95.

(11) Dillard, R. D.; Yen, T. T.; Stark, P.; Pavey, D. E. *J. Med. Chem.* **1980**, *23*, 717.

(12) (a) Harfenist, M.; McGee, D. P. C.; White, H. L. *J. Med. Chem.* **1991**, *34*, 2933. (b) Harfenist, M.; McGee, D. P. C.; White, H. L.; Cooper, R. B.; Davidson, R. B. T. Eur. Pat. Appl. 1991, EP 419,157; *Chem. Abstr.* **1991**, *115*, 29349. (c) McGee, D. P. C.; White, H. L.; Johnson, T. F.; Harrelson, J. C.; Harfenist, M.; Reeves, M. D.; Chandrasurin, P. PCT Int. Appl. WO 9204,897; U.S. Appl. 1992, 583,916; *Chem. Abstr.* **1992**, *117*, 151021.

(13) Lee, H. H.; Palmer, B. D.; Boyd, M.; Baguly, B. C.; Denny, W. A. *J. Med. Chem.* **1992**, *35*, 258.

(14) Beck, J. R. *Tetrahedron* **1978**, *34*, 2057.

(15) (a) Preston, P. N.; Tennant, G. *Chem. Rev.* **1972**, *72*, 627. (b) Radl, S. *Janssen Chim. Acta* **1993**, *11*, 12. (c) Li, W.-S.; Thottathil, J.; Murphy, M. *Tetrahedron Lett.* **1994**, *35*, 6591. (d) Li, W.-S.; Thottathil, J. *Tetrahedron Lett.* **1994**, *35*, 6595.

(16) Buncel, E.; Menon, B. C. *J. Am. Chem. Soc.* **1980**, *102*, 3499.

(17) Strauss, M. J. *Ind. Eng. Chem. Prod. Res. Dev.* **1979**, *18*, 158.

(18) Strauss, M. J.; DeFusco, A.; Terrier, F. *Tetrahedron Lett.* **1981**, *22*, 1945.

(19) (a) Ghosh, P. B.; Whitehouse, M. W. *J. Med. Chem.* **1968**, *11*, 305. (b) Whitehouse, M. W.; Ghosh, P. B. *Biochem. Pharmacol.* **1968**, *17*, 158. (c) Ghosh, P. B.; Ternai, B.; Whitehouse, M. W. *J. Med. Chem.* **1972**, *15*, 255.

(20) Niclas, H. J.; Zoelch,L. Ger. (East) DD 284,232; *Chem. Abstr.* **1992**, *115*, 29341.

(21) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, *57*, 97.

(22) Beugelmans, R. *J. Org. Chem.* **1994**, *59*, 5535.

(23) Sanger, F. *Biochem. J.* **1945**, *39*, 507.

(24) (a) Bunnett, J. F.; Hermann, D. H. *Biochemistry* **1970**, *9*, 816. (b) Barra, M.; De Rossi, R. H. *J. Org. Chem.* **1989**, *54*, 5020.

(25) (a) Imai, K. *Anal. Chim. Acta* **1981**, *130*, 377. (b) Watanabe, Y.; Imai, K. *Anal. Biochem.* **1981**, *116*, 471. (c) Watanabe, Y.; Imai, K. *J. Chromatogr.* **1982**, *239*, 723.

(26) Matsson, O.; Persson, J.; Axelson, S.; Langstrom, B. *J. Am. Chem. Soc.* **1993**, *115*, 5288.

(27) (a) Kirk, K. L.; Crevling, C. R. *Med. Res. Dev.* **1984**, *4*, 189. (b) Coenen, H. H. In *Synthesis and Applications of Isotopically Labelled Compounds 1988*; Baillie, T. A., Jones, J. R., Eds.; Elsevier: Amsterdam, 1989; pp 443–448. (c) Eckelman, W. C. In *Synthesis and Applications of Isotopically Labelled Compounds 1991*; Buncel, E., Kabalka, G. W., Eds.; Elsevier: Amsterdam, 1992; pp 13–21. (d) Stone-Elander, S.; Elander, N. In *Synthesis and Applications of Isotopically Labelled Compounds 1991*; Buncel, E., Kabalka, G. W., Eds.; Elsevier: Amsterdam, 1992; pp 648–651.

(28) Plenevaux, A.; Lemaire, C.; Palmer, A. J.; Danhaut, P.; Comar, D. *Appl. Radiat. Isot.* **1992**, *43*, 1035.

(29) Clark, J. H.; Bauemont, A. J.; Beochat, N. Eur. Pat. Appl. 1993, EP 534,317; *Chem. Abstr.* **1993**, *119*, 72323.

(30) Vlasov, V. M. *J. Fluorine Chem.* **1993**, *61*, 12.

(31) Wang, X. C.; Kalaritis, P.; Chang, M. L. PCT Int. Appl. WO 93 09,077; *Chem. Abstr.* **1993**, *119*, 138892.

(32) Takashi, I.; Nagata, K.; Ogata, M.; Ohsawa, A. *Chem. Pharm. Bull.* **1993**, *41*, 220.

(33) Makosza, M.; Wrobel, Z. *Heterocycles* **1992**, *33*, 585.

(34) Stahly, G. P.; Stahly, B. C.; Lilje, K. C. *J. Org. Chem.* **1984**, *49*, 578.

(35) Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions. The Chemistry of Anionic Sigma Complexes*; Elsevier:Amsterdam, 1984.

(36) (a) Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667. (b) Bernasconi, C. F. *MTP Int. Rev. Sci. Org. Chem. Ser. 1*, **1973**, *3*, 33. (c) Artamkina, G. A.; Egorov, M. P.; Beletskaya, I. P. *Chem. Rev.* **1982**, *82*, 427. (d) Terrier, F. *Chem. Rev.* **1982**, *82*, 77.

(37) Stahly, G. P.; Stahly, B. C.; Maloney, J. R. *J. Org. Chem.* **1988**, *53*, 690.

(38) (a) Makosza, M.; Ludwiczak, S. *J. Org. Chem.* **1984**, *49*, 4562. (b) Makosza, M.; Glinka, T. *J. Org. Chem.* **1983**, *48*, 3861. (c) Makosza, M.; Owczarczyk, Z. *J. Org. Chem.* **1989**, *54*, 5094. (d) Makosza, M.; Sienkiewicz, K. *J. Org. Chem.* **1990**, *55*, 4979.

(39) Stahly, G. P. *J. Fluorine Chem.* **1989**, *45*, 431.

(40) Strauss, M. J.; Torres, R.; Phelan, J.; Craft, A.; Pitner, B.; Nason, D.; Carignan, Y.; Dust, J. M.; Buncel, E. *Can. J. Chem.* **1987**, *65*, 1891.

(41) Dust, J. M.; Harris, J. M. *J. Polym. Sci. Chem. A* **1990**, *28*, 1875.

(42) (a) Cooke, M. P.; Archer, B. G.; Krakauer, H. *Biochem. Biophys. Res. Commun.* **1974**, *57*, 1032. (b) Dust, J. M.; Secord, M. D. *J. Phys. Org. Chem.*, in press.

(43) Shalati, M. D.; Overberger, C. G. *J. Polym Sci., Part A: Polym. Chem.* **1981**, *21*, 3425.

(44) (a) Mati, S.; Mandal, B. K. *Prog. Polym. Sci.* **1986**, *12*, 11. (b) Fukawa, I.; Tanabe, T.; Dozono, T. *J. Chem. Soc., Perkin Trans. 2* **1992**, 377.

(45) Shaffer, T. D. *J. Polym. Sci., Part C: Polym. Lett.* **1989**, *27*, 457.

(46) (a) Delfort, B.; Lucotte, G.; Cormier, L. *J. Polym. Sci., Part A: Polym. Chem.* **1990**, *28*, 2451. (b) Lucotte, G.; Cormier, L.; Delfort, B. *J. Polym. Sci., Part A: Polym. Chem.* **1991**, *29*, 897.

(47) Mani, R. S.; Zimmerman, B.; Bhatnagar, A.; Moranty, D. K. *Polymer* **1993**, *34*, 171.

(48) Percec, V.; Clough, R. S.; Rinaldi, P. L.; Litman, V. E. *Macromolecules* **1991**, *34*, 5889.

(49) Ree, K. C.; Evers, E. H. G.; Van den Berg, M. *Toxicol. Environ. Chem.* **1988**, *17*, 171.

(50) (a) Humppi, T.; Heinola, K. *J. Chromatog.* **1985**, *331*, 410. (b) Humppi, T. *Chemosphere* **1986**, *15*, 2003.

(51) (a) Kende, A. S.; Wade, J. J.; Ridge, D.; Pohland, A. *J. Org. Chem.* **1974**, *39*, 931. (b) Kende, A. S.; de Camp, M. F. *Tetrahedron Lett.* **1975**, 2877.

(52) (a) Gray, A. P.; Cepa, S. P.; Cantrell, J. S. *Tetrahedron Lett.* **1975**, 2873. (b) Gray, A. P.; Cepa, S. P.; Simon, I. J.; Aniline, O. *J. Org. Chem.* **1979**, *41*, 2435.

(53) (a) Tiernan, T. O.; Wagel, O. J.; Garrett, J. H.; Van Ness, G. F.; Solch, J. G.; Harden, L. A.; Rogers, C. *Chemosphere* **1989**, *18*, 835. (b) Tiernan, T. O.; Wagel, D. J.; Van Ness, G. F.; Garrett, J. H.; Solch, J. G.; Rogers, C. *Chemosphere* **1989**, *19*, 573.

(54) (a) Brunelle, D. J.; Singelton, D. A. *Chemosphere* **1983**, *12*, 183. (b) Brunelle, D. J.; Singleton, D. A. *Chemosphere* **1985**, *14*, 173.

(55) (a) Foster, R. A. *J. Phys. Chem.* **1980**, *84*, 2135. (b) Slifkin, M. A. *Mol. Interact.* **1981**, *2*, 271.

(56) (a) Buncel, E.; Symons, E. A. *Can. J. Chem.* **1966**, *44*, 771. (b) Buncel, E.; Zabel, A. W. *J. Am. Chem. Soc.* **1967**, *89*, 3082. (c) Buncel, E.; Symons, E. A. *J. Org. Chem.* **1973**, *38*, 1201. (d) Buncel, E.; Zabel, A. W. *Can. J. Chem.* **1981**, *59*, 3177.

(57) (a) Russell, G. A.; Janzen, E. J. *J. Am. Chem. Soc.* **1964**, *86*, 1807. (b) Russell, G. A.; Danen, W. C. *J. Am. Chem. Soc.* **1968**, *90*, 347.

(58) Crampton, M. R.; Davis, A. B.; Greenhalgh, C.; Stevens, J. A. *J. Chem. Soc., Perkin Trans. 2* **1989**, 675.

(59) De Vargas, E. B.; Setti, E. L.; Aimar, M. L.; De Rossi, R. H. *J. Org. Chem.* **1993**, *58*, 7364.

(60) (a) Bacaloglu, R.; Blasko, A.; Bunton, C. A.; Ortega, F.; Zucco, C. *J. Am. Chem. Soc.* **1992**, *114*, 7708. (b) Bacaloglu, R.; Blasko, A.; Bunton, C. A.; Dorwin, E.; Ortega, F.; Zucco, C. *J. Am. Chem. Soc.* **1991**, *113*, 238. (c) Bacaloglu, R.; Blasko, A.; Bunton, C. A.; Ortega, F.; Zucco, C. In *Atual. Fis.-Quim. Org., [Conf. Latinoam. Fis.-Quim. Org.]* **1991**, *1*, 165 (Humeres, E., Ed.). (d) Bacaloglu, R.; Bunton, C. A.; Ortega, F. *Int. J. Chem. Kinet.* **1988**, *20*, 195. (e) Bacaloglu, R.; Bunton, C. A.; Cerichelli, G.; Ortega, R. *J. Am.*

Chem. Soc. **1988**, *110*, 3495. (f) Bacaloglu, R.; Bunton, C. A.; Cerichelli, G. *J. Am. Chem. Soc.* **1987**, *109*, 621.
(61) (a) Simonin, M. P.; Halle, J. C.; Terrier, F.; Pouet, M. J. *Can. J. Chem.* **1985**, *63*, 866. (b) Terrier, F.; Debleds, F.; Halle, J. C.; Simonin, M. P. *Tetrahedron Lett.* **1982**, *23*, 4079. (c) Simonin, M. P.; Pouet, M. J.; Terrier, F. *J. Org. Chem.* **1978**, *43*, 855. (d) Alaruri, A. D. A.; Crampton, M. R. *J. Chem. Res. (S)* **1980**, 140; *(M)* **1980**, 2157. (e) Bernasconi, C. F. *J. Am. Chem. Soc.* **1971**, *93*, 6975. (f) Bernasconi, C. F. *J. Am. Chem. Soc.* **1970**, *92*, 4685. (g) Foster, R. A.; Fyfe, C. A.; Emslie, P. H.; Foreman, M. I. *Tetrahedron* **1967**, *23*, 227. (h) Meisenheimer, J. *Justus Liebigs Ann. Chem.* **1902**, *323*, 205. (i) Jackson, C. J.; Gazzolo, P. H. *J. Am. Chem. Soc.* **1900**, *23*, 376. (j) Strauss, M.; Torres, R. *J. Org. Chem.* **1989**, *54*, 756. (k) Renfrow, R. A.; Strauss, M. J.; Terrier, F. *J. Org. Chem.* **1980**, *45*, 471. (l) Jackson, C. L.; Boos, W. F. *Am. Chem. J.* **1898**, *20*, 444.
(62) (a) Servis, K. L. *J. Am. Chem. Soc.* **1967**, *89*, 1508. (b) Servis, K. L. *J. Am. Chem. Soc.* **1965**, *87*, 5495.
(63) Norris, A. R. *Can. J. Chem.* **1969**, *47*, 2895.
(64) Caveng, P.; Zollinger, H. *Helv. Chim. Acta* **1969**, *50*, 681.
(65) Fyfe, C. A.; Damji, S. W. H.; Koll, A. *J. Am. Chem. Soc.* **1979**, *101*, 951.
(66) Chamberlin, R.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1993**, 75.
(67) Chamberlin, R. A.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1994**, 425.
(68) (a) Crampton, M. R.; Routledge, P. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 573. (b) Chamberlin, R. A.; Crampton, M. R.; Robotham, I. A. *J. Chem. Res. (S)* **1994**, in press.
(69) (a) Akopojivi, R. E.; Emokpae, T. A.; Hirst, J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 443. (b) Onyido, I.; Hirst, J. *J. Phys. Org. Chem.* **1991**, *4*, 367.
(70) Bunnett, J. F.; Garst, R. H. *J. Am. Chem. Soc.* **1965**, *87*, 3875.
(71) Bunnett, J. F.; Orvik, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 2417.
(72) Hasegawa, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1314.
(73) Bunnett, J. F.; Sekiguchi, S.; Smith, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 4865.
(74) Fujinuma, H.; Hosokawa, M.; Suzuki, T.; Sato, M.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1969.
(75) (a) Hirst, J.; Onuoha, G. N.; Onyido, I. *J. Chem. Soc., Perkin Trans. 2* **1988**, 971. (b) Bamkole, T. O.; Hirst, J.; Onyido, I. *J. Chem. Soc., Perkin Trans. 2* **1982**, 889.
(76) Akinyele, E. T.; Onyido, I.; Hirst, J. *J. Phys. Org. Chem.* **1990**, *3*, 41.
(77) Banjoko, O.; Otiono, P. *J. Chem. Soc., Perkin Trans. 2* **1981**, 399.
(78) (a) Nudelman, N. S.; Palleros, D. *J. Org. Chem.* **1983**, *48*, 1607. (b) Nudelman, N. S. *J. Phys. Org. Chem.* **1989**, *2*, 1.
(79) (a) Capon, B.; Rees, C. W. *Ann. Rep. Prog. Chem.* **1963**, *20*, 279. (b) Hirst, J. *J. Phys. Org. Chem.* **1994**, *7*, 68.
(80) Crampton, M. R.; Routledge, P. J.; Golding, P. *J. Chem. Soc., Perkin Trans. 2* **1984**, 939.
(81) Brooke, D. N.; Crampton, M. R.; Corfield, C. G.; Golding, P.; Hayes, G. F. *J. Chem. Soc., Perkin Trans. 2* **1981**, 526.
(82) Brooke, D. N.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1850.
(83) Buncel, E.; Norris, A. R.; Proudlock, W. *Can. J. Chem.* **1968**, *46*, 2759.
(84) (a) Atherton, J. H.; Crampton, M. R.; Duffield, G. L.; Andrews, J. A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 443. (b) Crampton, M. R.; Stevens, J. A. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1715. (c) Cox, J. P. L.; Crampton, M. R.; Wight, P. *J. Chem. Soc., Perkin Trans. 2* **1988**, 25. (d) Crampton, M. R.; Kee, T. P.; Wilcock, J. R. *Can. J. Chem.* **1986**, *74*, 1714.
(85) Buncel, E.; Dust, J. M.; Jonczyk, A.; Manderville, R. A.; Onyido, I. *J. Am. Chem. Soc.* **1992**, *114*, 5610.
(86) (a) Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* **1977**, *14*, 133. (b) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.
(87) Manderville, R. A.; Buncel, E. *J. Am. Chem. Soc.* **1993**, *115*, 8985.
(88) Manderville, R. A.; Buncel, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1887.
(89) Bernasconi, C. F.; Muller, M. C. *J. Am. Chem. Soc.* **1978**, *100*, 5530.
(90) (a) Buncel, E.; Manderville, R. A. *J. Phys. Org. Chem.* **1993**, *6*, 71. (b) Buncel, E.; Eggimann, W. *J. Am. Chem. Soc.* **1977**, *99*, 5958. (c) Buncel, E.; Webb, J. G. K.; Wiltshire, J. F. *J. Am. Chem. Soc.* **1977**, *99*, 4429. (d) Buncel, E.; Eggimann, W. *Can. J. Chem.* **1976**, *54*, 2436. (e) Buncel, E.; Jonczyk, A.; Webb, J. G. K. *Can. J. Chem.* **1975**, *53*, 3761. (f) Buncel, E.; Webb, J. G. K. *J. Am. Chem. Soc.* **1973**, *95*, 8470.
(91) Shein, S. M.; Byval'kevich, O. G. *Zh. Org. Khim.* **1972**, *8*, 328.
(92) (a) Shein, S. M.; Byval'kevich, O. G.; Khemlinskaya, A. D. *Zh. Org. Khim.* **1976**, *12*, 134. (b) Machacek, V.; Sterba, V.; Lycka, A.; Snobl, D. *J. Chem. Soc., Perkin Trans. 2* **1982**, 355. (c) Buncel, E.; Moir, R. Y.; Norris, A. R.; Chatrousse, A. P. *Can. J. Chem.* **1981**, *59*, 2470.
(93) Buncel, E.; Tarkka, R. M.; Dust, J. M. *Can. J. Chem.* **1994**, *72*, 1709.
(94) Biggi, G.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1980.
(95) Crampton, M. R.; Stevens, J. A. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1097.
(96) Bernasconi, C. F.; Gandler, J. R. *J. Org. Chem.* **1977**, *42*, 3387.
(97) Ainscough, J. B.; Caldin, E. F. *J. Chem. Soc.* **1956**, 2538.
(98) Cooney, A.; Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1973.
(99) Crampton, M. R.; Gibson, B.; Gibson, F. W. *J. Chem. Soc., Perkin Trans. 2* **1979**, 91.
(100) Buncel, E.; Dust, J. M.; Manderville, R. M.; Tarkka, R. A. Unpublished work.
(101) Clapp, L. B.; Lacey, H.; Beckwith, G. G.; Srivastava, R. M.; Muhammad, N. *J. Org. Chem.* **1968**, *33*, 4262.
(102) Terrier, F.; Millot, F.; Morel, J. *J. Org. Chem.* **1976**, *41*, 3892.
(103) Terrier, F.; Millot, F. *Bull. Soc. Chim. Fr.* **1970**, 1743.
(104) Buncel, E.; Murarka, S. K.; Norris, A. R. *Can. J. Chem.* **1984**, *62*, 534.
(105) Bernasconi, C. F. *J. Org. Chem.* **1971**, *36*, 1671.
(106) (a) Buncel, E.; Norris, A. R.; Russell, K. E.; Tucker, R. *J. Am. Chem. Soc.* **1972**, *94*, 1646. (b) Buncel, E.; Norris, A. R.; Russell, K. E.; Sheridan, P.; Wilson, H. *Can. J. Chem.* **1974**, *52*, 1750. (c) Buncel, E.; Norris, A. R.; Russell, K. E.; Sheridan, P.; Wilson, H. *Can. J. Chem.* **1974**, *52*, 2306.
(107) Fyfe, C. A.; Malkiewich, C. D.; Damji, S. W. H.; Norris, A. R. *J. Am. Chem. Soc.* **1976**, *98*, 6983.
(108) Brooke, D. N.; Crampton, M. R. *J. Chem. Res. (S)* **1980**, 340; *(M)* **1980**, 4401.
(109) Hasegawa, Y. *J. Org. Chem.* **1985**, *50*, 649.
(110) Terrier, F.; Aw-Kow, G.; Pouet, M. J.; Simonnin, M. P. *Tetrahedron. Lett.* **1976**, 227.
(111) (a) Buncel, E.; Renfrow, R. A.; Strauss, M. J. *J. Org. Chem.* **1987**, *52*, 488. (b) Buncel, E.; Dust, J. M.; Park, K. T.; Renfrow, R. A.; Strauss, M. J. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; Adv. Chem. Ser. 215, American Chemical Society: Washington, DC, 1987; pp 369–378. (c) Buncel, E.; Dust, J. M. *Can. J. Chem.* **1988**, *66*, 1712. (d) Dust, J. M.; Buncel, E. *Can. J. Chem.* **1991**, *69*, 978. (e) Dust, J. M.; Buncel, E. *Can. J. Chem.* **1994**, *72*, 218.
(112) (a) Di Nunno, L.; Florio, S.; Todesco, P. E. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1469. (b) delRosso, M. D.; DiNunno, L.; Florio, S.; Amorese, A. *J. Chem. Soc., Perkin Trans. 2* **1980**, 239.
(113) Buncel, E.; Chuaqui-Offermanns, N.; Norris, A. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 415.
(114) (a) Aw-Kow, G. *C. R. Hebd. Seances Acad. Sci. Ser. C.* **1978**, *287*, 231. (b) Terrier, F.; Chatrousse, A. P.; Millot, F. *J. Org. Chem.* **1980**, *45*, 2666. (c) Terrier, F.; Millot, F.; Chatrousse, A. P.; Pouet, M. J.; Simonnin, M. P. *Org. Magn. Reson.* **1976**, *8*, 56.
(115) Buncel, E.; Chuaqui-Offermanns, N.; Hunter, B. K.; Norris, A. R. *Can. J. Chem.* **1977**, *55*, 2852.
(116) Crampton, M. R.; Routledge, P. J.; Golding, P. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1621.
(117) Crampton, M. R.; Routledge, P. J.; Corfield, C. G.; King, R. M.; Golding, P. *J. Chem. Soc., Perkin Trans. 2* **1982**, 31.
(118) Murto, J. *Acta Chem. Scand.* **1966**, *20*, 297.
(119) Hasegawa, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2186.
(120) Bowden, K.; Nadvi, N. S. *J. Chem. Soc., Perkin Trans. 2* **1987**, 189.
(121) Bunnett, J. F.; Gisler, M.; Zollinger, H. *Helv. Chim. Acta* **1982**, *65*, 63.
(122) Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1442.
(123) Byrne, W. E.; Fendler, E. J.; Fendler, J. H.; Griffin, C. E. *J. Org. Chem.* **1967**, *32*, 2506.
(124) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147.
(125) (a) Bunnett, J. F.; Buncel, E. *J. Am. Chem. Soc.* **1961**, *83*, 1117. (b) Bunnett, J. F.; Buncel, E.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1962**, *84*, 4136. (c) Buncel, E.; Onyido, I. *Can. J. Chem.* **1986**, *64*, 2115. (d) Cox, R. A.; Onyido, I.; Buncel, E. *J. Am. Chem. Soc.* **1992**, *114*, 1358.
(126) (a) Bolton, R.; Hamilton, D. G.; Sandell, J. P. B. *J. Chem. Soc., Chem. Commun.* **1990**, 917. (b) Bolton, R.; Hamilton, D. G.; Sandell, J. P. B. *J. Chem. Soc., Perkin Trans. 2* **1991**, 431. (c) Bolton, R.; Pilgrim, A. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1745. (d) Bolton, R.; Pilgrim, A. J. *Aust. J. Chem.* **1993**, *46*, 1119.
(127) Baughman, E. H.; Krevoy, M. M. *J. Phys. Chem.* **1974**, *4*, 421.
(128) Bicknell, R. T. M.; Davies, D. B.; Lawrence, K. G. *J. Chem. Soc., Faraday Trans. 1* **1982**, *78*, 1595.
(129) (a) Bordwell, F. G.; Cripe, T. A.; Hughes, D. L. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; Adv. in Chem. Ser. Vol. 215, American Chemical Society: Washington, DC, 1987; pp 137–153. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
(130) (a) Crampton, M. R.; Gold, V. *J. Chem. Soc.* **1964**, 4293. (b) Crampton, M. R.; Gold, V. *J. Chem. Soc. (B)* **1966**, 893.
(131) Crampton, M. R. *Adv. Phys. Org. Chem.* **1969**, *7*, 211.
(132) Bartoli, G.; Todesco, P. E. *Acc. Chem. Res.* **1977**, *10*, 125.
(133) Guedira, N. E.; Beugelmans, R. *J. Org. Chem.* **1992**, *57*, 5577.
(134) (a) Crampton, M. R.; Khan, H. A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1173. (b) Crampton, M. R.; Gibson, B.; Gilmore, F. W. *J. Chem. Soc., Perkin Trans. 2* **1979**, 91. (c) Castilho, P. C. M. F.; Crampton, M. R.; Yarwood, J. *J. Chem. Soc., Perkin Trans. 2* **1991**, 639.
(135) Destro, R.; Grammicioli, C.; Simonetta, M. *Acta Crystallogr. B.* **1968**, *24*, 1369.

(136) Fendler, J. L.; Hinze, W. L.; Liu, L. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1768.
(137) Murphy, R. M.; Wulff, C. A.; Strauss, M. J. *J. Am. Chem. Soc.* **1974**, *96*, 2678.
(138) (a) Hine, J. *J. Am. Chem. Soc.* **1963**, *85*, 3239. (b) Hine, J.; Mahone, L. G.; Liotta, C. L. *J. Am. Chem. Soc.* **1967**, *89*, 5911.
(139) (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer Verlag: Berlin, 1983; pp 9–11, 82, 90, and 135–136. (b) Sinnott, M. L. *Adv. Phys. Org. Chem.* **1988**, *24*, 114. (c) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 5–20.
(140) Bernasconi, C. F.; Howard, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 7248.
(141) (a) Bunnett, J. F.; Cartano, A. V. *J. Am. Chem. Soc.* **1981**, *103*, 4861. (b) Sekiguchi, S.; Aizawa, T.; Tomoto, N. *J. Org. Chem.* **1981**, *49*, 93. (c) Sekiguchi, S.; Suzuki, T.; Hosakawa, M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1783.
(142) (a) Sekiguchi, S.; Hosakawa, M.; Suzuki, S.; Sato, M. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1111. (b) Sekiguchi, S.; Suzuki, S.; Hirosawa, Y.; Ishikura, H. *J. Org. Chem.* **1990**, *55*, 1829. (c) Sekiguchi, S.; Ishikura, H.; Hirosawa, Y.; Ono, N. *Tetrahedron* **1990**, *46*, 5567.
(143) (a) De Vargas, E. B.; Remedi, M. V.; De Rossi, R. H. *J. Phys. Org. Chem.* **1995**, *8*, 113. (b) De Vargas, E. B.; De Rossi, R. H. *J. Phys. Org. Chem.* **1989**, *2*, 507. (c) De Vargas, E. B.; De Rossi, R. H.; Veglia, A. V. *J. Org. Chem.* **1986**, *51*, 1967. (d) De Rossi, R. H.; De Vargas, E. B. *J. Am. Chem. Soc.* **1981**, *103*, 1533.
(144) Epiotis, N. D. *Theory of Organic Reactions*; Springer Verlag: Berlin, 1978.
(145) Terrier, F.; Goumont, R.; Pouet, M. J.; Boubaker, T.; Halle, J. C. *Pol. J. Chem.* **1994**, *68*, 2415.
(146) Ueda, J.; Sakabe, N.; Tanaka, J.; Furusaka, F. *Bull. Chem. Soc. Jpn.* **1963**, *41*, 2866.
(147) Makosza, M.; Glinka, A.; Kinowski, A. *Tetrahedron* **1984**, *40*, 1863.

CR950237R